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Ulcerative Colitis in the Age of the Id

By Sherman M. Mellinkoff*

AN INTELLIGENT NEW INTERN had just finished examining a patient with acute ulcerative colitis. The sudden onset of bloody diarrhea, the latter's persistence for eight weeks, the pus-laden stool and the sigmoidoscopic counterpart of red velvet seemed all in order. But the intern was puzzled. "I can't figure out what great love she has lost, and she doesn't seem to have the right personality," he said. "Either she has something else, or I've missed something."

This recent occurrence illustrates a popular and growing conviction that the cause of ulcerative colitis is a psychiatric disturbance, and its corollary, that a healthy personality structure (whether achieved by ignorance, accident, or the couch) is not compatible with an angry colonic mucosa. So appealing has this view become that the term "ulcerative colitis" is, to many patients (including physicians suffering from the disease) an accusation rather than a diagnosis. The indictment is greeted in the doctor's dining room or in any respectable country club with a spontaneous and enthusiastic probing for Oedipus or Electra. One or the other can generally be located, to a chorus of Q.E.D.'s or of urgent borborygmi, as the case may be.

The present thesis is not that psychiatric factors are unimportant in ulcerative colitis. To make such an assertion would be to contradict the eyes and ears of those who see the disease daily. Furthermore, since the etiology of ulcerative colitis is still in open season for argument, it is difficult to reject dogmatically a psychiatric basis as the cardinal cause. The intention here is rather to separate what appears to *influence the course* of the disease from what *causes* the disease, and to explore some of the consequences of failure to make this distinction.

Upon what evidence did the puzzled intern, or his mentors, conclude that ulcerative colitis is caused by emotional disturbances? First, it is well known that emotions powerfully influence the function of the bowel and the appearance of its mucosa.¹ Certain vulgar expressions are recorded in novels about the Second World War as testimony that the panic of

battle may provoke urgent or involuntary defecation in healthy men. Most of us have had at least a gentle reminder of this natural law on such inconvenient occasions as a final examination. Second, psychiatrists have found certain personality traits and life situations in patients with ulcerative colitis, and many physicians are familiar with the morbidly sick individual whose infantile hostility no less than his fever and bloody stools is the consternation of an entire ward. Third, while bold probing psychotherapy is usually an invitation to catastrophe, gentle counsel and friendly support may be accompanied by victory over the disease, or a bearable truce, and thus may obviate colectomy.

These observations seem to me to justify the conclusion that an understanding of the patient's emotional problems and needs and a sympathetic and reassuring approach to them may be of great help in the treatment of ulcerative colitis. They also pose many important questions about the physiology of the gastrointestinal tract and the relationship between the latter and man's thoughts. But they do not, I submit, in any sense of the word prove that ulcerative colitis is *caused* by emotional tension. It would be equally easy (and equally wrong), were we unaware of atherosclerosis, to say that emotional tensions are the cause of Heberden's angina.

To accept a theory is to watch for its predicted manifestations. In fact, it is in this manner that a theory establishes its validity, and it may be that a theory has no other value and cannot, in a final and eternal sense, be "proved." But to watch for predicted manifestations is sometimes to ignore, or simply not to discover, phenomena that are not easily explained by the motivating theory. So it sometimes seems to me with the theory that ulcerative colitis is a psychogenic disease. The holder of this theory is likely to be unfamiliar with the ambulatory patients whose mild but unmistakable ulcerative colitis is healed completely or well controlled without the necessity of hospitalization. Many of these patients appear, to the amateur at least, to be emotionally vastly different from the so-called "typical hospital case," and, indeed, frequently from one another. Recently a florid case of ulcerative colitis was found in a Mongolian idiot.²

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What secret sorrows she had we shall never know, but to all appearances she was a happy, sheltered and much loved imbecile.

On the other side of the same coin one recalls patients whose personalities are classical for "typical ulcerative colitis," but in whom the disease is absent. One such patient, a woman, gave a history indicative of so-called nervous diarrhea over a period of twenty years, but the closest scrutiny failed to uncover a scintilla of evidence for inflammatory disease of the bowel.

Suppose that ulcerative colitis is greatly influenced but not caused by psychic trauma. What difference does it make? Why should anyone bother to question the widely held opinion that ulcerative colitis is a psychogenic disease? Two reasons suggest themselves. The first is that an open mind, rather than a mind made up, is more likely to solve what is thus far still an unsolved mystery, a common illness frequently leading to invalidism and sometimes to death. If the new interns do *not* know the cause of ulcerative colitis they may better be able to look for the cause. If they believe the cause is known, they will be less inclined to look.

The second reason for advocating indecision where no decision has yet been found is a therapeutic one. Certainty as to causation often fixes the approach of the therapist. One who believes, for example, that ulcerative colitis is always caused by a food allergy will invariably treat his patients with an elimination diet. One who believes that ulcerative colitis is always caused by pathogenic bacteria will probably use several antibiotics. And one who is convinced that ulcerative colitis is the direct result of emotional conflicts will orient treatment in that

direction. I have no doubt that these and other regimens are sometimes followed by healing, but until we know what causes ulcerative colitis we will not know how much of the healing is due to the treatment and how much to the natural course of the disease. On the other hand, one sometimes sees patients with ulcerative colitis in whom emaciation has been allowed to appear partially as a result of preoccupation with a restrictive diet, or because the patient has been so intent upon resolving some social or inner conflict that he has been ambulatory with a considerable fever and has been too exhausted to eat well. In a debilitating disease subject to spontaneous (or unexplained) remissions and exacerbations it would seem wise to use whatever measures improve nutrition. If the latter can be accomplished in a given case by amelioration of a trying social situation, so much the better. But if, in another case, focusing attention upon a marital incompatibility to which the patient is irrevocably committed is only going to spoil his appetite, we do well not to insist upon finding so active a psychotherapeutic approach. If such adaptive tactics mean abandoning a fixed concept of the cause of ulcerative colitis, perhaps Shakespeare's advice is applicable: "Drain not the bitter cup of prophecy." Uncertainty is a difficult state of mind to cultivate, but let it not be said of any of us, "He is frequently in error, but never in doubt."

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Cricket,* Critics, Conformity and Curmudgeonship

By Louis Lasagna†

AT A MEETING LAST YEAR of an eminent group of neurologists and psychiatrists, the following conversation occurred:

"What do you think of the meeting?"

"Awful! Never saw such a cordial bunch in my whole life."

This saturnine retort might be dismissed as a temporary fit of choler, did it not contain a valid criticism of modern American medical life, to wit, that we have become a community of comfortable, affable gentlemen.

It has long been evident that nonscientific attributes are important in shaping a doctor's career. From his first interview for college admission, a prospective physician is well advised to cultivate the esteem of his colleagues and, more especially, of his superiors. He need not "polish up the handle of the big front door," but he had better look to his shoes. Admissions officers have good reason, of course, to evaluate carefully those attributes of a student other than his intelligence quotient. There are probably more defections from medical school because of emotional problems, for example, than because of intellectual deficits.

Yet within the relatively broad limits encompassing those premedical students who can make the grade scholastically and emotionally in medical school, there is still considerable leeway for the atypical student, the "oddball," the nonconformist. How actively do medical schools search for these unusual men? (I do not refer to the unusual but obviously popular Phi Beta Kappa man with varsity letters in four sports.) How often do admissions committees go out of their way to attract or accept the "oddball"? Does the inclusion of one or two such "gambles" satisfy the requirements for a "balanced" class? The problem is admittedly complex. Some "oddballs" are hopeless schizophrenics; others are nonpsychotic but hardly the type one would want near sick people under *any* circumstances; etc., etc.

* Cricket, a form of periodic activity, is extremely popular among the male inhabitants of certain isolated areas of the civilized world. Generally classified as a sport, it appears to combine the qualities of athletic competition, folk dance, and religious rite. The rules of the game are essentially unintelligible to nonparticipants, but are scrupulously adhered to by the contestants, and infractions are extraordinarily rare.

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Notwithstanding the difficulties of the problem, medical school officers cannot avoid decisions about these atypical students for the simple reason that each year a class of students must be selected. Faced with a given "oddball," do you admit him, or not? How many can a school afford to enroll? How many can a school afford to reject? It is one thesis of this article that medical schools all too often consider nonconformist, off-the-beaten-path candidates unpertizing as potential physicians or medical scientists.

This proclivity is less disturbing than the exercise of similar bias in picking people for research positions, for fellowships, for permanent faculty posts, for professorships. Certainly there are positions (such as a chief medical resident) where a misanthropic, bull-in-a-china-shop personality and a successful performance are almost mutually exclusive. A similar (although in my opinion less strong) case might be made for department heads, who must deal with many kinds of people and many types of problems. But cannot everyone think of examples of successful department heads who are insufferable martinets, yet have proved fantastically effective teachers, or administrators, or both? Some extremely successful deans and hospital directors have been individuals whose faulty interpersonal relationships have led many to speculate at length on the possibility of canine ancestry on their maternal side. The ability to drink deeply at the well of knowledge is presumably more important for a professor than his capacity for bourbon old-fashionedness, no matter how felicitous the latter capacity may appear to his colleagues.

For research fellowships and research grants, the nonscientific qualities of the applicant would seem largely subsidiary. The primary question in such cases is (or should be): "Is the research worth doing, and can the person in question do a good job at the task he has set for himself?" It is, accordingly, unnerving to read applications in which the investigator (or his superior) has considered it vital to list the names and qualifications of his parents (the you-can-read - about - dad - in - Who's - Important - in - Medicine play), the endearing characteristics of his wife (the she's-a-den-mother-and-active-in-church-affairs play), his military exploits (the Wake-Island-task-force play), etc. One might paraphrase the reply of the Midwestern employer to some caste-conscious, Bostonian character references of a potential employee: "You misunderstood me—I wanted to hire the boy, not breed him."

Some months ago a national magazine¹ carried the grim story of a 4-day house party arranged by a

famous foundation to size up eleven prospective candidates. The idea behind the soiree was to throw together the selection committee and the candidates and afford an opportunity for communal food, drink, talk and sport. This living together in painful proximity would presumably reveal all sorts of sterling qualities in the appropriate men and unmask any cheaper alloys among the demi-candidates. But what (one might ask) of the socially ill-at-ease candidate? (A colleague of mine suggested that the guy with a limp handshake is probably out of luck. While there may be a strong correlation between firmness of handshake and research ability, it has not yet been established.)

Very depressing was the fact that the wives of the committee members, without access to any of the filed data on the candidates, picked the same "winners" as their husbands. This probably suggests not so much that the wives had unusual perspicacity, as it does the tendency for the husbands and wives to like the same kind of people. (It is hard to visualize Frank Lloyd Wright, Albert Einstein, or George Bernard Shaw at such a levee; it is even harder to imagine their being chosen as winners.)

One might counter that personal qualities are of importance where all the candidates have "equal" scientific appeal, but this latter situation probably seldom occurs. It might also be suggested that any equation utilized in reaching a decision will be heavily weighted in favor of scientific qualifications. It could be pointed out, however, that vermouth is present in dry martinis in amounts of only one-seventh* the quantity of gin, and yet a small excess of vermouth is often enough to override completely the most admirable of gins.

To be sure, "oddballness" is neither a sufficient nor a necessary condition for productivity or inspirational teaching. There are brilliant individuals who are also attractive, know a social amenity when they see one, and grace any festive board or cocktail party. Blessed are such people, and blessed their colleagues! There are other productive folk, however, who are depressive (and depressing), or arrogant, or thoughtless, or boring, or just generally disagreeable. The point at issue is whether we are to be distracted by nonessentials from devoting our attention to an individual's *pertinent merits and demerits*. We must eschew automatic acclaim of the wild iconoclast and the poseur; we must equally avoid insensate admiration of someone merely because he is pleasant, conventional, and unalarming.

Another reflection of a scientific "nice guy" policy is the paucity of forthright criticism in print or at public meetings. It is not considered good taste to correct a colleague who has committed a serious error or uttered some ridiculous nonsense. The arguments run as follows: (1) "The nonsense and error will be generally appreciated ultimately," and (2)

"To criticize means the probable loss of a friend, the likely acquisition of an enemy, and the inevitable risk of being considered an argumentative fool." One can even quote Holmes² in support: "Controversy equalizes fools and wise men . . . and the fools know it."

But is there really not justification for *encouragement* of provocative critiques? There is assuredly a large middle ground between sycophancy and polemic.[†] Since progress demands the ultimate consignment of most of today's "facts" to the rubbish heap of obsolescence, and since "the role of the disciple is always to betray the master,"³ why shouldn't the air be cleared as rapidly and effectively as possible? Granted that no one likes to be corrected, in a forced choice between an abraded ego and progress the ego must needs be sacrificed as a lesser good. It is to be hoped, nevertheless, that some modicum of restraint will usually prevail, so that while the atmosphere will not resemble a girl's school tea (jointly sponsored by the chaplain and the dean of women) it will also not simulate the last act of *Götterdämmerung*. (It must also be granted that at times a stunned silence at scientific meetings can be more devastating than strong talk.)

In other fields, such as art, music, the theatre, and literature, the influential critics are not those who apologetically wheedle their way through an opinion, but those who speak forcefully and to the point. Why not in medicine? It is true that medicine has no "professional" critics, and that a creative artist (i.e., investigator) may be restrained from attacking another creative artist lest he be accused of seeking personal gain via the denigration of a competitor. But even in the arts there is criticism of one artist by another, and such opinions are not necessarily less respected or effective than those of professional critics. It is also to be hoped that in all criticism, scientific or nonscientific, the relevance of the commentary will triumph over the appeal of the genetic fallacy. Furthermore, one can counter that there is a great need for honest talk, and that the price of silence perhaps outweighs the risks involved in speaking up. Nor should there be any concern lest the criticism be "merely destructive." As James Agate so aptly put it, "Whatever may be feasible in the domain of Lewis Carroll, in the world as we know it constructiveness is possible only before an event."⁴

In conclusion, one might paraphrase another wise observer of the modern scene, Jacques Barzun, and say that in "these tedious days of superficial fraternity" one must have "the will to sort out the *relevant* from the muck of the plausible which convention

* At our house.

† I shall avoid the question of whether a good healthy polemic isn't desirable from time to time.

automatically piles up around all things." If we are searching for research workers, or inspiring and stimulating teachers, we must not demand that such men comply with Procrustean standards of behavior, dress, etc. If we earnestly seek a brisk exchange of new ideas, and a jettisoning of scientific deadwood, we must be willing to take off our white kid gloves, come to grips with error and shibboleth, and heave them mercilessly overboard.

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2. HOLMES, O. W.: The Autocrat of the Breakfast Table.
3. MILLER, H.: The Cosmological Eye. Norfolk, New Directions, 1939.
4. AGATE, J.: The Later Ego. New York, Crown, 1951.

TO READERS AND CONTRIBUTORS

An Experiment in Medical Journalism

The policy of Clinical Research Proceedings is not only to give rapid publication to research abstracts, but also to provide a vehicle for kinds of articles which do not ordinarily find places in other publications.

These articles should be informed but brief statements of *views*, and they may cover a wide variety of professional matters. Their subject matter will range from purely scientific questions to discussions of research in general and of the environment in which research is carried on. Some of them will be solicited, but we hope that interested authors will submit such material of their own accord. The views expressed may well be somewhat partisan, and we expect that they will evoke counter-statements by workers who are not in agreement with them. A conscientious effort will be made to publish as many of these statements as space allows in early succeeding issues. Such contributions are of course subject to the customary editorial discretion.

Summary reviews of the usual type and original research communications (apart from abstracts) will not ordinarily be acceptable for the Journal, since numerous publication opportunities for such contributions already exist.

The aim of the policy is to provide a meeting place for medical minds, such that the membership of the American Federation for Clinical Research, and other interested persons, may benefit from the enormous amount of careful thought, unsupported by specific laboratory data, that is now being given to important professional issues by competent and conscientious workers. We would like our content to be often controversial without being contentious, and to point occasionally to worthwhile objectives without crusading.

The Editor and his associates solicit the advice and good will of readers of Clinical Research Proceedings. The development of this experiment in medical journalism must depend on the willingness of competent persons to express themselves in print, and also on the willingness of readers of conviction to write in opposition to or in support of communications in the Journal. Such expression of opinion may take the form of "Letters to the Editor," and it is our hope that there will be an active Correspondence Section. Suggestions for changes in plan or for new activities will be welcomed.—David T. Graham

NOTICES

Forthcoming Meeting

The eleventh annual meeting of the Western Society for Clinical Research will be held Thursday afternoon, Friday morning, and Saturday morning, January 30th through February 1, 1958, at Carmel-by-the-Sea, California.

Information regarding the meeting may be obtained from Arthur J. Seaman, M.D., Secretary-Treasurer, Western Society for Clinical Research, University of Oregon Medical School, Portland 1, Oregon.

New Research Tools

The information reported here is obtained from manufacturers. All notices and inquiries should be addressed to **New Research Tools Editor, Samuel N. Turiel & Associates, Inc., 750 N. Michigan Ave., Chicago 11, Ill.** Include name(s) of the manufacturer(s).

♦ **Electronic integrator and timing system** with synchronizing units, designed for use with standard oscillograph recorders. Developed to meet the requirements of psychophysiological investigators, it is readily expandable. Any variable which is a function of time can be fed into the system and automatically integrated. Medical Electronics Development Co.

♦ **Instruments for gas and vapor-phase chromatography** by elution. They are designed for analysis of most gases and volatilized liquids, and contain a new, highly-sensitive detector cell. Burrell Corp.

♦ **Two-pan analytical projection balance**, with semi-circular housing, weight dials, projection reading and air damping. The light metal beam is adjusted for constant sensitivity throughout the entire range of the balance. C. A. Brinkmann and Co.

♦ **Source calibrator**, designed for quick determination of the activity content of liquid or solid sources of radioactive isotopes. Activities ranging from 5 microcuries to 500 millicuries can be measured in one of the two well-type ionization chambers. Tracerlab, Inc.

♦ **Improved scintillation detector**, to permit pulse height analysis. Tracerlab, Inc.

♦ **New body scanner**, for mapping specific organs or localizing neoplastic lesions through radioactivity. Instrument has fully automatic controls, with recording in constant view. It is available either with a standard scaler or a pulse height analyzer and highly collimated detector. NRD Instrument Co.

♦ **Multi-range, multi-channel thermistor thermometer**. Total range of the instrument is divided into segments, and each segment is presented as a full scale range on the indicator, to preserve the accuracy of each range. There are 6 thermistor circuits, each with an outlet jack. Cole-Parmer Instrument & Equipment Co.

Obituary

The National Office has been notified of the death of the following member:

Dr. Joseph G. Hamilton, Berkeley, California, February, 1957.

PROGRAM, MIDWESTERN SECTION

AMERICAN FEDERATION FOR CLINICAL RESEARCH

Thursday, October 31, 1957

Thorne Hall, Northwestern University, Chicago, Illinois

Dr. Robert P. Gilbert, Presiding

Presentations will be limited to ten minutes

9:00 a.m.

1. **The Coronary Circulation in the Anemic Human Subject.**
Carl Kobelt, Raymond C. Christensen,* John W. Ord,* Rhoda Powsner,* Takashi Wada,* Timothy J. Regan and Harper K. Hellem.* Detroit. *page 292*
2. **Retrograde Hepatic Vein Occlusion in Man: Hemodynamic and Radiographic Studies.**
Bernard L. Brofman. Cleveland. *page 303*
3. **Experimental Studies on the Effects of Protein and Carbohydrate on Hypercholesterolemia and Atherogenesis in Cockerels on a High Fat-High Cholesterol Ration.**
Jeremiah Stamler, R. Pick† and L. N. Katz (assisted by D. Friedman and P. Johnson).* Chicago. *page 296*
4. **Hypothermia Effects on Extremity Circulation in the Dog.**
Charles A. Hamilton and Roderick R. Landers* (introduced by Robert L. Grissom).* Omaha. *page 295*
5. **Enhancement of Antihypertensive Drug Effect by Electrolyte Depletion.**
F. A. Tapia, R. E. Schneckloth* and H. P. Dustan.* Cleveland. *page 293*
6. **Chlorothiazide—Physiological Connecting Link.**
*Archer P. Crosley, Jr. and Robert E. Cullen.** Madison. *page 307*

INTERMISSION (10 Minutes)

Refreshments Courtesy of G. D. Searle & Co.

7. **The Effects of 5-Hydroxytryptophan, the Precursor of Serotonin, in Experimental Animals and Man.**
John D. Davidson, Albert Sjoerdsma, Ladd N. Loomis* and Sidney Udenfriend.** Bethesda. *page 304*

* By Invitation

† Senior Member

8. **Depressed Renal Function in the Carcinoid Syndrome: Effects of Serotonin in Normal Subjects and of an Anti-Serotonin (Bromo-LSD).**

R. E. Schneckloth, I. H. Page† and A. C. Corcoran.†* Cleveland. *page 308*

9. **The Absorption, Distribution and Excretion of Mecamylamine in Rats and Man.**
M. D. Milne, R. C. Muehrcke, G. G. Rowe* and K. Somers.** Chicago *page 293*
10. **The Effect of Maternal Thyroid Function on Fetal Thyroid Function and Development.**
Edward A. Carr, Jr., William H. Beierwaltes, Govind Raman, Norma Spafford* and John Tanton.** Ann Arbor. *page 296*
11. **A Comparison of the Effects of Tolbutamide and Insulin on Peripheral Glucose Metabolism in Man.**
James W. Craig, Valerie J. Molzahn, William R. Drucker, Max Miller† and Hiram Woodward, Jr.** Cleveland. *page 298*
12. **Comparison of the Effects of Insulin and Orinase (Tolbutamide) on Peripheral Glucose Utilization in the Dog.**
Leonard L. Madison and Roger H. Unger. Dallas. *page 298*

1:00 p.m.

LUNCHEON AND BUSINESS MEETING

Abbott Hall Dining Room and Thorne Hall

2:00 p.m.

13. **The Clinical Importance of Ultrafiltrable Calcium Determination.**
Ananda S. Prasad and Edmund B. Flück.† Minneapolis. *page 301*
14. **The Nature of the Coagulation Defect in Pseudothrombophilia B.**
Shirley A. Johnson, Raymond W. Monto† and John W. Rebutck.** Detroit. *page 291*

15. **A Study of the Coagulation Defect in Thrombocythemia.**
Irving A. Friedman, Harold B. Shifter, Joseph H. Robbins* and Arthur B. Dupee.**
 Chicago. page 291
 16. **Failures in the Maintenance Therapy of Pernicious Anemia with an Oral Preparation of Vitamin B₁₂ and Intrinsic Factor.**
Leif G. Suhrland, David Rubin, Gordon Meacham* and Austin S. Weisberger.†* Cleveland.
page 290
 17. **Hereditary Methemoglobinemia.**
*Anthony V. Pisciotta and Jean E. Hinz.** Milwaukee.
page 291
 18. **Neonatal Hepatitis, a Genetic Study.**
David Yi-Yung Hsia, Joseph D. Boggs, Shirley G. Driscoll* and Sydney S. Gellis.**
 Chicago. page 304
 20. **Protein Metabolism in Infection.**
Eric Reiss. St. Louis. page 300
 21. **Natural Resistance to Respiratory Infections in Naval Recruits. I. Properdin Levels in Relation to the Immunization Program.**
Irwin Schultz and Gene H. Stollerman. Great Lakes, Illinois. page 304
 22. **The Effects of Chest Irradiation on Pulmonary Function.**
Stanford K. Sweany, William T. Moss* and Francis J. Haddy.* Chicago. page 310
 23. **Blood Flow Through a Distended Lung.**
*M. H. Weil, W. S. Fowler† and Makoto Murao.** Rochester, Minnesota. page 310
 24. **Diffusing Capacity of Pulmonary Membrane and Pulmonary Capillary Blood Volume in Normal Subjects; the Effects of Exercise and Body Position; Preliminary Observations in Cardiac Patients.**
Benjamin M. Lewis, Tai-hon Lin, Richard Komisaruk* and Frances E. Noe.** Detroit. page 309
- INTERMISSION (10 Minutes)
19. **Potassium Depletion in Cirrhotic Patients.**
Richard E. Peterson, Bartis M. Kent and James J. O'Toole.** Iowa City. page 303

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Advance Reports Submitted to the Annual Meeting of the
Midwestern Section
of the
American Federation for Clinical Research

Thorne Hall, Chicago, Illinois • Thursday, October 31, 1957

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BLOOD

Correlation of Simultaneous Serum Iron Determinations with Red Cell Indices and Estimations of Marrow Iron Stores

By *Norman A. Nelson, Newton K. Ressler, Harold L. Oster and Samuel D. Jacobson*. Department of Medicine, Wayne County General Hospital, Eloise, Michigan.

The value of estimating marrow hemosiderin as an aid in assessing body stores of iron has been emphasized by Finch, Beutler, and others. The technic and results reported in the literature have varied considerably. Nevertheless, estimation of hemosiderin has been urged as an integral part of the marrow examination. The studies to be described were undertaken in an attempt to relate this to other indices of iron balance.

Approximately 50 patients, presenting indications for marrow examination, were included in this study. The serum iron was determined by either the method of Ramsey or that proposed by Ressler and Zak. In the majority of cases, the unsaturated iron binding capacity was also estimated. Red cell indices were obtained at the time of marrow aspiration, all counts and hemoglobin determinations being performed by the same technician using calibrated pipettes. Leishman-stained marrow smears were first evaluated for their content of macrophages, and then stained for iron, according to the method of Sundberg and Broman. Marrow particle sections stained for iron were also examined. Oral iron tolerance tests, serum copper determinations, iron stains of other tissues, and therapeutic trials were performed in selected patients.

Marrow sections and smears were of approximately equal value in demonstrating marrow hemosiderin. In only 12 out of 50 examinations were both sections and smears negative for nonhemoglobin marrow iron. These were correlated with low serum iron levels and hemoglobin concentration of erythrocytes (M.C.H.C.). We would agree with Stevens, Colman and Finch that failure to demonstrate non-hemoglobin marrow iron in adequate preparations represents an abnormality and suggests the presence of either an overt or an occult iron deficiency state.

Enhancement of Vitamin B₁₂ Uptake by Rat Liver Slices in the Presence of Hog Intrinsic Factor Concentrate

By *Victor Herbert and Irving M. London*. Department of Medicine, Albert Einstein College of Medicine-Bronx Municipal Hospital Center, New York.

An enhancement of Co⁶⁰-labeled vitamin B₁₂ uptake by rat liver slices incubated at 37°C. in the presence of a hog intrinsic factor concentrate (HIFC) has been reported by Miller, Raney, and Hunter. In studies on the mechanism of uptake of vitamin B₁₂ by the liver, we have found that, at a concentration of 830 µg. of Co⁶⁰-B₁₂/mm. of Hastings bicarbonate medium, the addition of HIFC, 0.26 µg./ml. of medium, was associated with up to a tenfold enhancement of Co⁶⁰-B₁₂ uptake by rat liver slices incubated at 37°C. (The HIFC used was Lederle Laboratories fraction WES 655 provided by Williams and Ellenbogen, and was active in a daily

oral dose of 1.0 mg. in urinary excretion tests of the Schilling type).

Enhancement was also observed on incubation of the slices with HIFC at 3°C., but did not occur if either the HIFC or the slices were heated at 100°C. for 10 minutes prior to incubation at 37°C.

Replacement of the calcium content of the medium with an equivalent millimolar concentration of sodium or potassium prior to incubation resulted in failure of HIFC to increase $\text{Co}^{60}\text{-B}_{12}$ uptake. The addition of versene to the medium, after enhancement of $\text{Co}^{60}\text{-B}_{12}$ uptake with HIFC, resulted in release of a major fraction of the $\text{Co}^{60}\text{-B}_{12}$ from the rat liver slices.

No increase in $\text{Co}^{60}\text{-B}_{12}$ uptake by rat liver slices was demonstrated on addition to the incubation medium of heparin, chondroitin sulfate, or orosomucoid, either in concentrations of 0.26 $\mu\text{g.}$ or of 8.3 $\mu\text{g./ml.}$ of incubation medium.

It remains to be determined what the physiologic significance of the increased uptake of vitamin B_{12} by liver slices in the presence of HIFC may be, and whether this effect is attributable to intrinsic factor or to some other substance present in HIFC.

Failures in the Maintenance Therapy of Pernicious Anemia with an Oral Preparation of Vitamin B_{12} and Intrinsic Factor

By *Leif G. Suhrland, David Rubin, Gordon Meacham and Austin S. Weisberger.* Cleveland.

The simultaneous oral administration of vitamin B_{12} and intrinsic factor has produced satisfactory hematologic and clinical response in pernicious anemia in relapse. The present study was undertaken to determine whether such a preparation would be effective in the long-term management of pernicious anemia.

Thirty-nine patients with pernicious anemia in remission were included in this study. Of this group, 23 were treated with 30 $\mu\text{g.}$ of vitamin B_{12} parenterally every four weeks and served as controls. Sixteen patients were treated daily with an oral preparation containing 1 $\mu\text{g.}$ of vitamin B_{12} and 18 mg. of intrinsic factor.

The patients treated with parenteral vitamin B_{12} were maintained in complete remission for a 3-year period. During this same period, five of the 16 patients treated with the oral preparation exhibited an unequivocal hematologic relapse. The duration of oral treatment preceding these relapses varied from 6 to 32 months. In two patients who suffered relapse, no response was noted even when the daily dose was increased twofold. Prompt remission followed parenteral vitamin B_{12} therapy. The remaining 11 patients have been maintained satisfactorily with the oral preparation for more than 36 months. Neurologic or lingual relapses were not encountered.

Preliminary studies with radioactive vitamin B_{12} and intrinsic factor indicate that patients who

relapsed absorbed less B_{12} than patients who were well maintained, despite the administration of the same amount of intrinsic factor.

Thus, an oral preparation of vitamin B_{12} and intrinsic factor was found to be ineffective as maintenance therapy in 30% of patients so treated. It is possible that a determination of the amount of radioactive B_{12} absorbed in the presence of a commercial source of intrinsic factor may be necessary for the selection of those patients suitable for maintenance therapy with an oral preparation.

Adaptation of the Antiglobulin Test for Use with Tannic Acid Treated Erythrocytes

By *Kenneth P. Mathews.* Department of Internal Medicine, University of Michigan Medical School, Ann Arbor.

Results of the antiglobulin (Coombs) test are not meaningful when tannic acid treated erythrocytes are used, since these cells nonspecifically take up normal serum globulins. Attempts to exhaust tanned red blood cells' ability nonspecifically to pick up globulin by preliminary incubation with several proteins were unsuccessful, but employing serum or plasma from a suitable species for this purpose has proved useful. The procedure is as follows: (1) tanned RBC plus (2) antigen (3) followed by preliminary incubation with serum or plasma of species A (4) followed by exposure to specific antiserum of species B (5) followed by testing with anti-globulin serum prepared by injecting species A with serum globulin of species B. Alternatively, whole serum or plasma from a third species (C) may be used for preliminary incubation in step (3), provided the antiglobulin serum used in the last step (5) is first neutralized with serum from this third species (C).

Studies employing a system involving egg albumin (Ea) sensitized tanned RBC, preliminary incubation with human serum or plasma, exposure to rabbit anti-Ea serum and testing with hen anti-rabbit globulin serum neutralized with normal human serum have yielded specific reactions in substantial titers (e.g., 1:3200). However, there is considerable variability in the ease with which the nonspecific uptake of globulin from different rabbit sera can be inhibited by human serum or plasma. In instances where the amount of the latter required to produce complete inhibition becomes too large to be practical, a differential agglutination titer can be obtained by comparing results with and without preliminary neutralization of the specific antiserum by direct addition of antigen.

The reproducibility of the results is good, though the test is distinctly less sensitive than the direct tanned cell technic (Boyden). It has been developed to study human allergic antibodies which fail to give direct agglutination of tanned erythrocytes sensitized with allergens.

Hereditary methemoglobinemia is ordinarily due to a congenital absence of methemoglobin reductase. However, it appears that in this family an equilibrium was established wherein increased intracorporeal methemoglobin resulted because of excessive formation of methemoglobin. While the mechanism has not yet been defined, it is possible that these patients are extraordinarily sensitive to oxidizing substances normally present in the blood.

Hereditary Methemoglobinemia

By *Anthony V. Pisciotto and Jean E. Hinz*, Department of Medicine, Marquette University School of Medicine and Milwaukee County General Hospital, Milwaukee.

This report deals with a family of Italian descent who were studied because of hereditary cyanosis. The index case, a 25-year-old woman and her 4-year-old son were cyanotic since birth. A second son, normal at birth, became cyanotic six months later coincident with the disappearance of fetal hemoglobin. A third son has remained normal. The woman's parents, siblings and husband showed no abnormality; this suggests the occurrence of a mutation.

Methemoglobin, demonstrated by spectrophotometric examination of the hemolysate, was present in a constant proportion of 30% of hemoglobin in the three affected persons. Methemoglobin concentration remained constant when their erythrocytes were incubated in fresh plasma or glucose in vitro. In contrast, methemoglobin in erythrocytes obtained from normals intoxicated with acetanilid, or obtained by treating normal erythrocytes with nitrite, was spontaneously reduced to oxyhemoglobin when incubated in vitro under the same experimental conditions. When the patients' erythrocytes were treated with sodium nitrite in vitro, a methemoglobin concentration of 90% resulted. When incubated with fresh normal plasma, the concentration fell to 30% in four hours. This demonstrates a hemoglobin-reducing mechanism in their erythrocytes. On the other hand, when the patients' erythrocytes were incubated with sodium nitrite, the rate of methemoglobin formation greatly exceeded that of normal erythrocytes treated under the same condition.

The Nature of the Coagulation Defect in Pseudohemophilia B

By *Shirley A. Johnson, Raymond W. Monto and John W. Rebeck*.

Pseudohemophilia B (Quick) is a mild to moderate hemorrhagic disease showing a familial tendency occurring in either sex and characterized by a prolonged bleeding time and poor prothrombin consumption. The mechanism of the abnormal bleed-

ing has been postulated to be on the basis of a vascular defect, platelet functional abnormality, or lack of a plasma factor.

Prothrombin consumption was found to be poor (below 20 sec.) in 10 patients suffering from pseudohemophilia B. When an assay for platelet factor 3 activity (Alkjaersig, Abe, and Seegers) was carried out, very little was found in platelets of these patients as compared with platelets of normal individuals. The addition in vitro of purified platelet factor 3 of bovine origin corrected the prothrombin consumption of patients with pseudohemophilia B. The morphology of normal platelets has been compared to those of patients with pseudohemophilia utilizing the electronmicroscope.

Cortisone and prednisone therapy did not alter the prothrombin consumption in pseudohemophilia B. Investigation is underway to prepare platelet factor 3 of bovine origin for intravenous use in patients with pseudohemophilia B. The administration of platelet factor 3 to thrombocytopenic patients resulted in a marked increase in vascular resistance. Assay for platelet factor 3 in relatives of patients with pseudohemophilia B may afford an opportunity to establish the genetics of this hemorrhagic disorder.

These preliminary studies suggest that pseudohemophilia B is a hemorrhagic disease resulting from a deficiency of platelet factor 3.

A Study of the Coagulation Defect in Thrombocythemia

By *Irving A. Friedman, Harold B. Shifter, Joseph H. Robbins and Arthur Dupee*.

Three patients who presented hemorrhagic manifestations and displayed thrombocythemia were studied before and after radioactive phosphorus therapy. Coagulation studies, including serum prothrombin, were normal, but the bleeding times were prolonged. Thromboplastin generation tests (TGT) were frequently abnormal when the standard number of platelets was employed, and were almost always abnormal when the platelets were highly concentrated. Control tests using normal platelets in high concentration behaved normally in the TGT.

In all three patients with standard platelet concentrations and in two patients with high platelet concentrations, the abnormality with TGT was corrected by the substitution of either normal serum or barium sulphate treated normal plasma in place of the patient's serum or plasma. The substitution of normal platelets in standard concentration partially corrected the defect occasionally.

Serum was obtained by reclothing (by recalcification) the patient's platelet-free plasma with normal or patient platelets. This serum, when introduced into the TGT, was capable of correcting the defect in two of the three patients tested, both at standard and high platelet concentrations.

After radioactive phosphorus therapy, when the

patient's platelet levels approached normal values and clinical improvement ensued, the bleeding time and TGT reverted to normal. However, when the platelets were highly concentrated in the TGT, the defect was still demonstrable and was still corrected by normal serum and plasma.

These findings suggest that the coagulation

defect in thrombocythemia involves serum and plasma factors, as well as quantitative and qualitative platelet alterations. While the mechanism for this interrelationship remains to be determined, our studies have ruled out prothrombin, accelerated globulin, proconvertin deficiency, as well as fibrinolysis, as responsible factors.

CARDIOVASCULAR SYSTEM

The Coronary Circulation in the Anemic Human Subject

By Carl Kobelt, Raymond C. Christensen, John W. Ord, Rhoda Powsner, Takashi Wada, Timothy J. Regan and Harper K. Hellem. Cardiovascular Laboratories, Departments of Medicine, Detroit Receiving Hospital and Dearborn V. A. Hospital, Wayne State University College of Medicine, Detroit.

To determine the coronary circulatory adjustments to anemia, six patients manifesting chronic secondary anemia with hemoglobins varying from 4.8 to 10.1 Gm. have been studied by the technic of coronary sinus catheterization. None of the patients showed clinical or hemodynamic evidence of heart failure.

Coronary blood flow ranged from 105 to 237 cc./100 Gm./min. with a mean of 146 ± 18.0 (S.E. M.), as compared to nonanemic individuals where the flow was 80.7 ± 2.43 cc./100 Gm./min. Brachial artery oxygen content averaged 8.22 ± 1.12 volumes %; coronary sinus oxygen content averaged 2.14 ± 0.49 volumes %; arterial coronary sinus oxygen difference averaged 6.09 ± 0.64 volumes %, there being, in the individual patient, a significant inverse relationship between these variables and the volume of coronary blood flow. Coronary resistance was decreased from the normal to 0.66 ± 0.16 mm. Hg/cc./100 Gm./min. ($P < 0.01$).

Left ventricular work was increased to 9.37 ± 2.41 Kg./min. and in the individual patient was not related to coronary flow. Myocardial oxygen consumption was within the normal range (8.43 ± 0.57 cc./100 Gm./min.) and in the individual patient showed no correlation to coronary flow. The calculated left ventricular mechanical efficiency was $44.3 \pm 4.25\%$, as compared to a normal of $33.8 \pm 2.21\%$ ($P < 0.05$).

Two patients were given 800 cc. of packed red blood cells in a one-hour period, causing a mean increase in hemoglobin of 2.8 Gm., an increase in cardiac output and work, with a discordant increase in myocardial oxygen consumption, resulting in a further increase of the already elevated left ven-

tricular efficiency. Coronary flow decreased 38 cc./100 Gm./min. in these two patients.

The data indicate that the heart in the anemic subject maintains a normal myocardial oxygen supply mainly by adjustments in volume of coronary blood flow but also by maximum oxygen extraction. There is a suggestion that the anemic heart has a higher mechanical efficiency than the normal.

Influence of Nalline upon Abnormal Cardiac Rhythms

By Timothy J. Regan and Harry Abramson. Cardiovascular Laboratory, Department of Medicine, Detroit Receiving Hospital, Wayne State University College of Medicine, Detroit.

The finding of a Nalline antagonism against steroid-induced cardiac arrhythmias in the dog (Cannon) has prompted a clinical study of its efficacy in digitalis-induced and spontaneous disorders of heart rhythm in cardiac patients who were on no other drug therapy. After obtaining repeated EKG controls for a period of one to three hours, 10 mg. every 15 minutes up to a maximum total of 40 mg. was rapidly administered intravenously with frequent EKG monitoring.

Two patients with digitalis-induced sinus bradycardia promptly accelerated their rate, reaching a maximum of about twice the control rate at 30 to 40 minutes, lasting six hours before resuming the control rate. Two patients with first degree A-V block following glycoside (PR. = .23-.24) reverted to normal PR with beginning effect in five minutes and maximum response at 30 to 50 minutes.

In a patient with a spontaneous 2:1 block and a ventricular rate of 39, a 1:1 response began to appear within two minutes and was constantly present at 45 minutes with a rate of 60. The block was again present on the subsequent day and Nalline reproduced the above result.

One patient treated on three occasions for either complete S-A block or A-V dissociation with complete block at a rate of 36 attained a regular sinus rhythm of 65 by forty minutes. On each occasion the block recurred 6 to 8 hours after Nalline. There was no therapeutic response in two patients

with digitalis intoxication, one with bigeminy and the other with a nodal rhythm of 90 which accelerated to 120 six minutes after Nalline.

The results in these 8 patients suggest that Nalline has a stimulatory action upon the S-A node, A-V node and the atria which is primary and not related to digitalis. This property resembles that of the sympathomimetics, but the tendency to ventricular ectopic beats after these agents was not observed after Nalline.

In addition, this drug had no effect on QRS duration and no significant effect on blood pressure. Preliminary studies indicate that the mild transitory respiratory acidosis and rise in pCO_2 subsequent to the drug do not mediate the therapeutic response.

The Absorption, Distribution, and Excretion of Mecamylamine in Rats and Man

By *M. D. Milne, R. C. Muehrcke, G. G. Rowe and K. Sommers*. Presbyterian-St. Luke's Hospital and University of Illinois College of Medicine, Chicago; the British Postgraduate Medical School, London, England; and the Department of Medicine and Cardiovascular Research Laboratory, University of Wisconsin, Madison.

Mecamylamine is a secondary amine used in the treatment of hypertension. Observations were made on its absorption, distribution, and excretion in man and animals.

Balance studies in patients with hypertension indicate that mecamylamine was completely absorbed from the gastrointestinal tract. Its distribution in the body was studied by injecting it intraperitoneally into rats. Analysis of various organs was made before and 6, 12, 18, and 24 minutes after injection. The highest concentrations were noted in the spleen; decreasing concentrations followed in the liver, lungs, kidney, heart, and skeletal muscle. Mecamylamine rapidly appeared within cells and in combination with nucleoproteins. This distribution is different from that of hypotensive agents, such as hexamethonium and pentolinium, which concentrate in the extracellular fluid. The intracellular concentration of mecamylamine is similar to what is seen with the antimalarial drugs, such as Mepacrine and chloroquin.

Eight hospitalized patients with severe hypertension were given steady maintenance doses (12.5 mg. to 37.5 mg./day) of mecamylamine. Serial observations were made simultaneously of blood pressure, urinary pH, and concentration of mecamylamine in the serum and urine. Studies were made during a period of acid urine excretion and later during a period of alkaline urine excretion. When the urine was strongly acid, large quantities of mecamylamine were found in the urine. This was accompanied by a rise in blood pressure. When the urine was very alkaline, only small quantities of mecamyl-

amine were excreted, and the blood pressure was reduced.

To study this phenomenon further, we injected 34 rats intraperitoneally (25 mg./Kg. body weight) twice daily for three days. Sixteen were given ammonium chloride to produce an acid urine. The remaining 18 were given Diamox or sodium bicarbonate to alkalize the urine. In the group excreting an alkaline urine, there was marked retention of mecamylamine, and 13 rats died in apparent hypotensive crisis. In the group which excreted an acid urine, only 2 deaths occurred. This difference is highly significant ($P < 0.001$).

Enhancement of Antihypertensive Drug Effect by Electrolyte Depletion

By *F. A. Tapia, R. E. Schneckloth and Harriet P. Dustan*. Research Division, Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland.

That antipressor effects of ganglion-blocking drugs are enhanced by sodium withdrawal is a general clinical impression. In order to document this impression, we observed 9 hospitalized patients with severe hypertension under prolonged treatment with ganglion-blocking drugs. The study consisted of a 3-4 control period, during which the requirement for the drug was established, a diuretic period of 4 days, during 3 of which diuretic doses of chlorothiazide were given, and a 3-4 day period of sodium repletion. The observations made daily were averages of 4 blood pressure readings (lying and standing), the dosage of blocking agent, body weight, urine volume, Na, Cl and K excretions. At the end of each phase, measurements were made of plasma volume and electrolytes and the blood pressure response to venous congestion of 3 extremities.

None of the 9 patients had signs of congestive failure; in all chlorothiazide caused diuresis with excess excretion of Na, Cl and K. In 5, who had previously followed a low-sodium diet, losses of 3-5% of body weight and 20-30% of plasma volume occurred; these changes were less evident in 2 out of 4 patients without previous Na restriction. In all, the average requirement of ganglion-blocking drug decreased by one-half or more, supine blood pressure was lower and postural hypotension was increased. During sodium repletion, blood pressure, body weight, plasma volume and drug requirement tended to return to control levels. No large changes were observed in plasma electrolyte concentrations or responses to venous occlusion.

The data suggest that decreased blood volume played a major role in the enhanced responses of these patients to ganglion-blocking drugs during electrolyte depletion. Therapeutically, sodium withdrawal may reduce drug requirement and, therefore, symptoms of parasympathetic blockade.

The Potentiation of Antihypertensive Therapy by Diuretics

By Allen C. Bullock, J. B. Rochelle and Ralph V. Ford. Baylor University College of Medicine and the V. A. Hospital, Houston, Texas.

The possible potentiating effects of long-term oral diuretics upon antihypertensive drugs was investigated. The purpose was to observe the effect of a chronically administered natriuretic agent, chlorazinin, in potentiating the effects of mecamlamine, a ganglionic blocking agent, given in combination with whole root *Rauwolfia serpentina*. It was postulated that the amount of mecamlamine required to achieve a therapeutic lowering of blood pressure would be substantially less if salt retention were decreased by the natriuretic agent. Concurrently, the feasibility of using oral diuretics, more precisely chlorazinin, in long-term therapy of hypertensive patients was investigated.

The clinical material was a group of outpatients with similar diagnoses of hypertensive cardiovascular disease with varying systemic involvement who had been observed previously on *Rauwolfia serpentina* and mecamlamine therapy and whose dosage of the drugs had been fairly well established. The patients were of two groups of 10 each, one receiving 300 mg. once and the other twice daily of chlorazinin. Many had had congestive failure previously, though none was in overt failure during the study. Only those with minimal or moderate renal disease or azotemia were selected. The patients were seen weekly, at which time lying and standing blood pressures, weight, BUN, WBC and hematocrit were obtained. After clinical evaluation their dose of mecamlamine was prescribed for the following week. All were receiving 400 mg. of *Rauwolfia serpentina* daily.

It was found that the natriuresis produced by chlorazinin, though accompanied by only moderate or negligible weight loss, definitely potentiated the effect of antihypertensive therapy and in nearly all instances made it possible to reduce the dosage of the drug required to produce optimal ganglionic blockade. These findings confirm the factor of salt retention in aggravating hypertension and demonstrates the usefulness of long-term oral diuretics in the management of hypertension. Effective ganglionic blockade with fewer of the side effects was achieved.

The Effect of Chronic Administration of Chlorothiazide (Diuril) (6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1,1-dioxide) in Man and the Production of Metabolic Acidosis by its Use

By Harold E. Zenisek and Walter M. Kirkendall. Medical Service, V. A. Hospital, and the Department of Medicine, State University of Iowa, Iowa City.

Chlorothiazide, a potent, oral diuretic of the carbonic-anhydrase inhibiting type, exerts a chloruretic effect during chronic administration. It has been used as daily supplemental therapy for arterial hypertension and congestive heart failure. When used chronically, metabolic acidosis has not been described.

We produced severe metabolic acidosis in a hypertensive woman by administering chlorothiazide daily for 8 days. She excreted significant amounts of urinary sodium throughout treatment. When nausea and agitation developed, we found the CO_2 content had fallen to 10 mEq./L. The BUN had risen from 18 to 32 mg.%. Chlorothiazide was stopped; urinary excretion of sodium decreased sharply for 3 days, and CO_2 content and BUN returned to normal in 2 days. Hypertension was unaltered.

We studied chronic chlorothiazide administration by giving it to a hypertensive man daily for 78 days in doses up to 4 Gm. per day. Serial observations were made on exchangeable sodium (E_{Na}), potassium (E_{K}), and chloride (E_{Cl}), renal excretion and serum levels of these electrolytes, glomerular filtration rate (C_{In}), effective renal plasma flow (C_{PAH}), and plasma pH CO_2 content, urine volume, body weight, and blood pressure. The patient had a prompt, significant fall in body weight (10 lbs.), blood pressure (36 mm. Hg mean pressure), serum potassium, and E_{K} , and a rise in $\text{E}_{\text{Na}}/\text{E}_{\text{K}}$ which persisted only until chlorothiazide was discontinued. Then, urinary excretion of electrolytes decreased sharply for 12 days. C_{In} and C_{PAH} fell 20% and 15% respectively and remained low 15 days after treatment. There was a transient rise in BUN during therapy.

Chronic administration of large doses of chlorothiazide produces sustained diuresis and may reduce hypertension significantly, but there are associated changes in body electrolytes and in renal function. Although it is an unusual complication, severe acidosis can be produced, perhaps by disproportionate loss of sodium retention of organic acids. Long-term, unsupervised use of this promising drug may be dangerous.

The Effects of Serotonin (5-hydroxytryptamine) upon Systemic, Pulmonary, and Coronary Hemodynamics and Metabolism

By George M. Maxwell, Cesar A. Castillo,* Douglas H. White, Jr.* and Charles W. Crumpton. Cardiovascular Research Laboratory and Departments of Medicine and Pediatrics, University of Wisconsin Medical School, Madison. (Supported in part by grants from the National Heart Institute, USPH, Wisconsin Heart Association and Wisconsin Alumni Research Foundation; Serotonin made available by the California Foundation for Biochemical Research, Los Angeles.)

Eighteen mongrel dogs were anesthetized with morphine sulfate (3 mg./Kg. I.M.) followed in one hour by pentobarbital (12 mg./Kg. I.V.). Control cardiac output (Fick) and coronary blood flow (N_2O application of Fick) were determined, 20 minutes allowed to elapse and serotonin creatinine sulfate administered by infusion through a catheter in the right atrium (20 μ g./Kg./min.). Five minutes after the serotonin administration was started, cardiac output and coronary flow measurements were repeated, during which time the infusion was continued.

Heart rate increased from 94 to 115/min., MABP decreased from 104 to 85 mm. Hg, and mean pulmonary artery pressure changed by +30%. Since cardiac output and stroke volume were unchanged, left ventricular work and total peripheral resistance decreased due to the change in MABP. Total pulmonary resistance and right ventricular work increased as a function of elevation of pulmonary artery pressure. An increase in ventilation was associated with a significant reduction in CO_2 content of arterial, mixed venous, and coronary sinus blood. Coronary flow increased from 71 to 85 cc./100 Gm./min. Coronary flow/beat was unchanged. Coronary vascular resistance decreased significantly. Coronary sinus oxygen content increased from 3.1 to 5.9 vol. %. Thus the decrease in myocardial oxygen extraction associated with the increase in coronary flow resulted in myocardial oxygen consumption remaining unchanged. Myocardial CO_2 excretion was maintained in a similar manner. The index of efficiency (left ventricular work/ $CMRO_2$) decreased. Coronary blood flow/left ventricular work ratio increased by 65%.

Under the experimental conditions described, serotonin acts as a peripheral and coronary vasodilator and has a vasoconstrictor effect upon the pulmonary vascular system. The decrease in coronary vascular resistance was associated with a reduction in MABP, increase in coronary flow, with myocardial oxygen consumption remaining unchanged. This is the pattern of a "benign" coronary vasodilator.

Hypothermia Effects on Extremity Circulation in the Dog

By Charles A. Hamilton and Roderick R. Landers.
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In order to better understand the important cardiovascular dynamics underlying circulatory failure during hypothermia, we undertook studies of peripheral circulation. Hypothermia was induced in 12 dogs in which observations of rectal (Tr), esophageal (Te), hind limb intramuscular (Tim) temperatures, mean arterial pressure (BPm), pulse (P), femoral arterial flows (Ffa), index of femoral re-

sistance (Rif), and Na_{24} clearance (k) from leg muscle sites were made.

Average temperatures were as follows: prehypothermia—Tim 35.1°C. in the left leg, Tim 34.7°C. in the right leg, Tr 36.5°C. and Te 36.6°C.; during the "stable" period of hypothermia Tim ranged from less than 20.0°C. to 28.9°C., Tr ranged from 25.9°C. to 30.8°C. (av. 28.7°C.), and Te ranged from 25.6°C. to 31.6°C. (av. 29.2°C.); immediately after rewarming—Tim 32.7°C. in left leg, Tim 31.9°C. in right leg, Tr 35.4°C. and Te 35.3°C.; following a secondary downward drift of temperature—Tim 26.1°C. in left leg, 25.7°C. in right leg, Tr 32.9°C. and Te 32.8°C.

Average circulatory parameters were as follows: prehypothermia—BPm 150 mm. Hg, P 138/min., Ffa (bubble flow method) 60 cc./min., Rif 2.4, and k 0.108; hypothermia—BPm 128 mm. Hg, P 110/min., Ffa 28 cc./min., Rif 6.9, and k 0.043; immediately after rewarming BPm 139 mm. Hg, P 155/min., Ffa 28 cc./min., Rif 7.2, and k 0.068; following a secondary downward drift of temperature—BPm 111 mm. Hg, P 118/min., Ffa 15 cc./min., Rif 11.4, and k 0.012. Tim was much lower and more variable than Tr or Te during hypothermia. Ffa varied from minute to minute during one period, and k values varied slightly at a given temperature level.

These data show that the dog is prone to (a) post-hypothermic circulatory failure as demonstrated by low mean blood pressure, increase in pulse, sustained diminished Ffa and k values, and (b) tendency to drift again toward hypothermia following artificial rewarming. Increased Rif during and after hypothermia, consistent with increased total peripheral resistance, was demonstrated.

The Effect of Suture Material in Determining the Patency of Artery Grafts Used as Replacements for Small Artery Segment

By John T. Phelan. Cardiovascular Research Laboratory and Department of Surgery, University of Wisconsin Medical School, Madison.

Initial observation on the failure of artery graft replacement of small artery segments suggested that thrombosis and occlusion occurred soon after implantation and in the majority of instances, the thrombus originated at the suture line and adjacent 2-3 mm. of the intima of the host artery.

Accordingly, we have investigated three different types of arterial suture material (5-0 silk, 5-0 nylon, and 5-0 Dacron) in performing the anastomoses between the artery graft and the host artery in an effort to determine what part, if any, the suture material plays in determining the patency of small artery grafts.

The carotid and femoral arteries of mongrel dogs were used in this investigation. In each instance the inside diameter of their arteries measured 4 mm. or less. Three different types of artery grafts were

employed: fresh autografts, fresh homografts, and preserved homografts. In each instance an end-to-end anastomosis, using an over-and-over suture was employed. The period of follow-up ranged from 3 days to as long as 3 months, at which time the animals were killed and the grafts examined.

The results of this investigation indicated that irrespective of the type of suture material, 90% of the fresh autografts remained patent. In addition, 50% of the fresh homografts were patent. However, the type of suture material did not appear to influence the end results with this group. In each instance, thrombosis and occlusion of the graft occurred when a preserved homograft was employed.

Experimental Studies on the Effects of Protein and Carbohydrate on Hypercholesterolemia and Atherogenesis in Cockerels on a High Fat-High Cholesterol Ration

By *J. Stamler, R. Pick and L. N. Katz*, with the assistance of *D. Friedman and P. Johnson*. Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago.

These studies were undertaken to assess inter-related effects of the three major dietary components—proteins, carbohydrates and fats—on cholesterolemia and atherogenesis. Five series of experiments were undertaken, utilizing 310 chicks. In every experiment, all birds were fed diets high in

fat and cholesterol (8% and 1% respectively). Lowering the protein content of the diet (from 20% by weight to 10–15%) consistently resulted in marked increase in hypercholesterolemia and atherogenesis (both aortic and coronary artery). A similar effect occurred when the ration was made deficient in methionine. Increasing the protein content of the diet significantly reduced the hypercholesterolemic and atherogenic response to the high fat-high cholesterol diet. This effect was obtained by adding a mixture of proteins to the mash, or by supplementing with a single fat-free protein source (e.g., soy protein, casein, albumen, fish flour, liver meal). With addition of sucrose (20–45% by weight) to the high fat-high cholesterol mash—resulting in a reduction of its protein content (to 15–10% by weight)—hypercholesterolemia and atherosclerosis were grossly increased. However, when these high fat-high cholesterol-high carbohydrate diets were brought up to 20% protein (by the addition of soy protein), no intensified hypercholesterolemia and atherogenesis were noted. Thus the deleterious effect of high sucrose was not a direct one, but rather an indirect consequence of the resultant reduction of protein intake. These findings pose the following question: In human populations ingesting high fat-high cholesterol rations, are cholesterolemia and atherogenesis influenced by the level of protein intake?

ENDOCRINES AND METABOLISM

The Effect of Maternal Thyroid Function on Fetal Thyroid Function and Development

By *E. A. Carr, Jr., William H. Beierwaltes, G. Raman, N. Spafford and J. Tanton*.

Bone x-rays suggest that cretinism begins in utero. Labeled thyroxine given in pregnancy shows little transplacental passage. It has been suggested that maternal hormone cannot overcome fetal hypothyroidism. Yet maternal hypothyroidism is commonly considered dangerous to the fetus.

We studied thyroid function of 15 mothers of cretins. Fourteen proved euthyroid. We measured I^{131} uptake and/or serum protein-bound iodine (PBI) in 5 pregnant and 8 nonpregnant female dogs and 21 newborn puppies (5 litters).

Excluding two dogs with high serum inorganic iodide concentrations, the mean PBI of nonpregnant and pregnant adult dogs was the same: 2.8 $\mu\text{g. \%}$ (S.E. = ± 0.3 and $\pm 0.4 \mu\text{g. \%}$, respectively). Three pregnant dogs were thyroidectomized 9, 19 and 50 days before spontaneous or operative delivery. Maternal PBIs at delivery were 1.8, 1.0 and 1.0 $\mu\text{g. \%}$, respectively. The newborn puppies' PBIs were 3.3, 3.8 and 5.2 $\mu\text{g. \%}$, respectively. The mean

puppy thyroid:muscle concentration of I^{131} , the I^{131} given to the first thyroidectomized mother 1 day before delivery, was 2350 (S.E. = ± 810). Five of 8 puppies of one thyroidectomized mother were underdeveloped in utero. Another's litter, followed 4 months postnatally, grew poorly.

Two nonthyroidectomized pregnant dogs received thyroxine orally for 9 and 14 days before delivery, raising maternal PBIs to 25 and 30 $\mu\text{g. \%}$, with the fetal PBI of the latter at 16 $\mu\text{g. \%}$. Both litters showed partial suppression of thyroid I^{131} uptake, mean thyroid:muscle ratios being 433 (S.E. = ± 289) and 240 (S.E. = ± 86), respectively. Iodine 131 crossed the placenta adequately, fetal:maternal serum I^{131} concentration ratios being 4.8 and 7.2 in 2 puppies.

Large doses of thyroxine, administered to the mother, give the fetus significant amounts of active hormone. Maternal hypothyroidism does not depress fetal serum PBI or thyroid activity but may inhibit intrauterine or postnatal development.

Human Thyroid Autoantibodies in Thyroid Disease

By *V. N. Dodson, W. H. Beierwaltes, A. H. Wheeler, N. R. Spafford, E. A. Carr, Jr. and G. H. Lowrey*.

Witebsky and Rose produced autoantibodies to rabbit thyroid extracts in rabbits and measured the titers by precipitin and complement fixation tests. The thyroid glands of these rabbits resembled Hashimoto's struma. Roitt and Doniach demonstrated autoantibodies to thyroid by precipitin test in the sera of patients with Hashimoto's disease.

To test the hypothesis that autoantibody against a patient's thyroid gland might produce myxedema, we have tested the sera of two proved hypothyroid adults. To test our hypothesis that thyroid defects resulting in cretinism might be caused by transplacental transfer from maternal serum to fetus, or by fetal autoantibodies against fetal thyroid, we have tested the sera of 14 cretins, their mothers, and 22 blood relatives of the cretins for controls. The cretins ranged in age from 6 weeks to 13 years. To test the hypothesis that stored thyroglobulin might be dumped into the circulation during surgical thyroidectomy and produce thyroid autoantibodies, we have tested the sera of two patients, 4 days, and 5 weeks, respectively, after surgical thyroidectomy. To test the hypothesis that hyperthyroid individuals might dump stored thyroglobulin into the circulation and subsequently develop autoantibodies to this "foreign" protein, we examined the sera of 3 hyperthyroid patients.

Precipitin and complement fixation tests against human thyroid antigen were the methods of assay of autoantibody titers. None of these sera has demonstrated significant titers, to date.

These negative findings are significant from the standpoint of technic because we have successfully demonstrated relatively high thyroid antibody titers in surgically proved human Hashimoto's struma and have successfully "immunized" rabbits against the same human thyroid antigen used in these studies. More patients will be added to each group and further refinements in antigen preparation are in progress.

Fractionated Plasma Protein Values in Subacute Thyroiditis

By Penn G. Skillern and Lena A. Lewis.

Stemmerman reported the occurrence of an increased concentration of serum alpha-2-globulin in 4 of 4 patients with subacute (granulomatous) thyroiditis. He suggested that this was an additional laboratory aid for the diagnosis of this disease.

Our purpose here is to present the results of Tiselius electrophoretic plasma protein analyses using barbital buffer in a series of 20 patients with subacute thyroiditis. Only 14 of these 20 patients had a significant elevation of the alpha-2-globulin value. Other findings were a decrease in the albumin values in 10 patients, elevation of the alpha-1-globulin values in 4 patients and beta-globulin values in 2 patients, and elevation of the gamma-globulin in 8 patients.

The alpha-2-globulin concentration was less likely to be elevated in those patients with subacute thyroiditis whose clinical febrile course was much less acute or in those who had only one thyroid lobe involved. Thus, the value of this test as a diagnostic aid seemed to be limited to those patients with a more typical clinical febrile picture. Only 3 of 50 patients with struma lymphomatosa and none of 30 patients with nontoxic adenomatous goiter had elevated alpha-2-globulin values. Also, the presence of a number of other systemic diseases or inflammations which may produce an elevated alpha-2-globulin value must be excluded. The elevation of the alpha-2-globulin value may be due to destruction of thyroid tissue and release of tissue protein, as observed in other types of inflammation, rather than to release of thyroglobulin alone. While an elevated alpha-2-globulin may be a useful aid in differentiating subacute thyroiditis from other types of goiter, we believe clinical and other laboratory aids are probably of more value.

Hyperparathyroidism Secondary to Renal Disease

By Victor E. Pollak, Albert F. Schneider, Gerhard A. Freund and Robert M. Kark. Departments of Medicine and Pathology, University of Illinois College of Medicine; and Department of Medicine, Presbyterian Hospital, Chicago.

The bone lesions which occur in chronic renal disease include rickets, osteomalacia, osteoporosis, osteosclerosis, and osteitis fibrosa. In reviewing the literature we were surprised to find only 25 cases of hyperparathyroidism secondary to renal disease that fulfilled the following criteria: (1) chronic renal disease, (2) hyperplasia of two or more parathyroid glands and (3) osteitis fibrosa. We therefore studied the hospital records of 91 consecutive cases dying of chronic renal disease with uremia over a period of 12 years. Seventeen cases of secondary hyperparathyroidism were found fulfilling the aforementioned criteria. In 12 the bone lesions were of mild or moderate severity; in 5 they were very severe.

The clinical and pathologic features of our cases and those from the literature were reviewed. The incidence of pyelonephritis was extremely high (32 out of 41); that of uncomplicated glomerulonephritis was low. Congenital renal lesions were found in 5. Ectopic calcification, especially of the arteries, was found in 25 cases, in all of whom the product $\text{Ca} \times \text{P}$ exceeded 30.

The patients were young, most of them dying in the second and third decades. The renal disease was of long duration, having been present for more than 10 years in 14 instances. Although these patients were uremic, the serum calcium was normal or elevated in 20 out of 34. The serum phosphorus was markedly elevated in only 9 and metabolic acidosis was severe in 7.

One patient, studied in detail, was thought to

have primary hyperparathyroidism with secondary renal disease. Severe chronic pyelonephritis was found by renal biopsy; the renal lesions of primary hyperparathyroidism were not seen. Postmortem, her illness was shown to be due to small congenital polycystic kidneys with superimposed severe acute and chronic pyelonephritis. The four parathyroids were greatly enlarged and there was severe osteitis fibrosa cystica.

The Diagnostic and Prognostic Significance of the Abnormal Oral Glucose Tolerance Test as Determined by Long-term Follow-up Studies

By *Roger H. Unger and Leonard L. Madison*. Department of Internal Medicine, University of Texas Southwestern Medical School, and V. A. Hospital, Dallas.

The long-term diagnostic and prognostic implications of abnormal oral glucose tolerance curves in persons with normal FBS's are uncertain. Some believe that deviations from the standards of the American Diabetes Association in properly prepared subjects, constitute specific evidence of diabetes mellitus. However, recent work indicates a high degree of nonspecificity of such abnormalities.

To study this problem, 110 persons were followed with oral GTT's for periods of from 5 to 7 years. Subjects were divided into categories according to their original GTT: (1) "Normal" (FBS < 100 mg. %; 1-hour < 150 mg. %; 2-hour < 100 mg. %); (2) "Intermediate": FBS < 100 mg. %, 1-hour > 150 mg. %, 2-hour > 100 mg. %; and (3) "Overtly Diabetic" (FBS > 100 mg. %, 1-hour > 150 mg. %, 2-hour > 100 mg. %).

Five to seven years later 65% of 54 "normals" still had "normal" GTT's, 33% had "intermediate" curves, and 2% were "overtly diabetic." Of 46 originally "intermediate" subjects, 28% now had "normal" GTT's, 57% remained "intermediate," and 15% had become "overtly diabetic." Of 10 "overtly diabetic" subjects, 80% remained diabetic and 20% were now "intermediate."

This suggests that, without fasting hyperglycemia, specificity of the abnormal GTT is low; 33% of normals became "intermediate" and only 15% of "intermediates" became overtly diabetic within 7 years. Furthermore, 28% of "intermediates" returned to normal, while more than half showed little change. Among "intermediates" who became overtly diabetic, the range of 1- and 2-hour blood sugar levels had been 180-224 mg. % (mean 195 mg. %) and 127-280 mg. % (mean 187 mg. %) respectively, compared to 150-203 mg. % (mean 158 mg. %) and 113-201 mg. % (mean 145 mg. %) respectively among "intermediates" who reverted to "normal."

It appears that, although the 5-7 year incidence of overt diabetes among "intermediates" is $7\frac{1}{2}$ times that of the "normal" group, the probability

of specificity for diabetes of an "intermediate" curve is low, but in general increases with the magnitude of the abnormality.

Comparison of the Effects of Insulin and Orinase (Tolbutamide) on Peripheral Glucose Utilization in the Dog

By *Leonard L. Madison and Roger H. Unger*. Department of Internal Medicine, University of Texas Southwestern Medical School, and V. A. Hospital, Dallas.

Stimulation of endogenous insulin secretion by the sulfonylureas is suggested by the failure to elicit the usual hypoglycemia in all preparations in which the β -cells are ablated (alloxanized, depancreatized and eviscerate animals). A formidable objection to this hypothesis is the lack of evidence indicating increased peripheral glucose utilization.

If the sulfonylureas stimulate insulin secretion, their effect on peripheral glucose utilization should mimic that of insulin. This study was designed to compare effects of intravenous insulin and tolbutamide on glucose utilization in 9 dogs by measuring changes in arteriovenous (A-V) glucose difference and A-V/arterial glucose concentration $\left(\frac{A-V}{A}\right)$.

Two experiments were performed on each dog: during one, glucagon-free insulin (.07 u/Kg.) was administered, and during the other, sodium-tolbutamide (30-60 mg./Kg.). Simultaneous femoral arterial and venous specimens were drawn every 5-15 minutes for $1\frac{1}{2}$ -3 hours. Glucose was analyzed by Somogyi's iodometric method on 2 cc. samples, thereby permitting valid measurement of A-V differences of 2 mg.

The results indicate a striking similarity of response in A-V difference and $\frac{A-V}{A}$ in each dog when insulin or tolbutamide was administered. Five dogs responded to insulin with moderate increases in A-V glucose (mean = 5 mg.) and in $\frac{A-V}{A}$ (mean = .07). These same dogs given tolbutamide showed changes of similar magnitude (6 mg. and .09 respectively). Four dogs manifested small increases in A-V glucose (mean 2.8 mg.) and $\frac{A-V}{A}$ (mean .04) after insulin and almost identical changes (2.6 mg. and .038) after tolbutamide.

These data indicating a similar effect of tolbutamide and insulin on peripheral glucose utilization are consonant with the hypothesis that tolbutamide stimulates endogenous insulin secretion.

A Comparison of the Effects of Tolbutamide and Insulin on Peripheral Glucose Metabolism in Man

By *James W. Craig, Valerie J. Molzahn, William R. Drucker, Max Miller and Hiram Woodward, Jr.*

Departments of Medicine and Surgery, Western Reserve University School of Medicine, Cleveland.

The mechanism of the hypoglycemic action of the sulfonylureas has not been explained satisfactorily. Several investigators have compared the metabolic effects of insulin and the sulfonylureas in an attempt to clarify the possible role of insulin in the hypoglycemic action of the latter compounds. One group reported that both intravenous insulin and tolbutamide increased the peripheral A-V glucose concentration difference, but this effect of the sulfonylureas has not been confirmed by others.

In the present study the direct effects of tolbutamide and insulin on glucose uptake in the forearm were compared by injecting the drugs into the brachial artery. Subjects were six male patients in each of whom the effects of both compounds were compared. Blood samples were obtained simultaneously from the brachial artery and a major antecubital vein both before and after injection of 0.2 or 0.4 Gm. of sodium tolbutamide (Orinase) or 0.01 unit/Kg. of insulin into the brachial artery. Insulin produced an increase in A-V glucose difference in 5 of the 6 subjects from a mean of 0 before injection to a mean of 6 mg./100 ml. during the first 30 minutes after injection. Tolbutamide produced no definite increase in A-V difference in any subject in the 30 minutes after injection, although arterial glucose fell 15 mg./100 ml. No direct stimulatory effect of tolbutamide on peripheral glucose uptake was demonstrated.

In 2 out of 3 cases in which peripheral A-V and hepatic venous-arterial glucose differences were determined simultaneously after injection of 2 Gm. of tolbutamide into a peripheral vein, the fall in arterial glucose was accompanied by a decreased splanchnic glucose output without an increase in peripheral A-V difference.

The Ballistocardiogram in Juvenile Diabetes Mellitus

By Robert Rakel and Thomas G. Skillman. Cardiac and Metabolism Laboratories, University of Cincinnati College of Medicine, Cincinnati.

Ballistocardiograms were obtained on 41 juvenile diabetic patients with a mean age of 24.5 years (range 15 to 43 years) and with a mean duration of diabetes for 17.5 years (range 8 to 30 years). Seventeen (41%) had abnormal tracings. There were 33 abnormal patterns distributed in seven categories. These were increased respiratory variation (5), abnormally small complexes (8), late downstroke pattern (6), early M pattern (4), increased transverse component (7), badly deteriorated complexes (2), and shallow K wave (1). The electrocardiogram was abnormal in only two of these 17 patients and in none of those with normal ballistocardiograms.

There was no relation of abnormal tracings to age, sex, duration of diabetes, insulin dosage, retinopathy, large vessel calcification, or concentration of blood glucose or serum total lipids. Heparin administered intravenously to four patients with hyperlipemia had no effect on abnormal patterns. However, in 14 of the 17 patients there was evidence of either nephropathy or hypertension. In two patients with abnormal ballistocardiograms who died, coronary atherosclerosis was found at autopsy.

A complete explanation for these abnormal ballistocardiographic patterns is not available. They are not typical of established coronary sclerosis, and the observations give no proof that coronary sclerosis was present in all instances. Nevertheless, it is suggested that the abnormalities may be related to the early development of coronary sclerosis.

Analysis of Factors other than Sodium and Chloride Maintaining Serum Osmolarity in Hyponatremic and Hypochloremic States in Rabbits

By Edwin G. Olmstead and Donald A. Roth. Departments of Medicine, Marquette University School of Medicine and Milwaukee County General Hospital, Milwaukee. (Aided by a grant from the Wisconsin Heart Association.)

This study was undertaken to evaluate factors ("X-factors") other than sodium and chloride contributing to serum osmolarity of rabbits during salt depletion and dilution of the extracellular fluid compartment.

Serum osmolarity was measured by freezing point depression (Δ^t). Contributions of sodium and chloride to Δ^t of serum was calculated from Δ^t of a serially diluted 0.155 M NaCl solution assuming similar ionization of NaCl in this solution and serum. Electroconductance of sera was measured by a conductance bridge with platinized electrodes at a 1 cm. distance. Serum water was determined gravimetrically by desiccation of serum at 105°C. for 24 hours.

In 30 control animals Na and Cl contributed 79.8% (S.D. = 2.8) and "X-factors" 20.2% (S.D. = 3) to the serum osmolarity. Mean specific conductance in this group was $126 \text{ mhos} \times 10^{-4}$ (S.D. = 12.5).

In 5 animals salt depleted by intraperitoneal dialysis with 20% glucose and water Na and Cl accounted for an average of 63.2% and "X-factors" for 36.6% of the serum osmolarity (after correction of Δ^t for added glucose). Mean specific conductance in this group was $101 \text{ mhos} \times 10^{-4}$.

In 5 animals salt depleted by intraperitoneal dialysis with 5% glucose and water Na and Cl accounted for a mean of 73.5% and "X-factors" for 23.1 of the osmolarity. Mean specific conductance was $118 \text{ mhos} \times 10^{-4}$.

In the 15 experimental animals electroconductance correlated best with the sum of the Na

and Cl ($r = 0.73$), but did not correlate with the Δ^1 of the serum ($r = -0.30$). There was no significant correlation of the sum of the Na and Cl with the Δ^1 of the serum ($r = 0.03$).

"X-factors" may contribute significant amounts to the serum osmolarity in rabbits during phases where Na and Cl are removed from the extracellular fluid compartment, but less significant amounts where Na and Cl are merely diluted by rapid intravenous infusion of 5% glucose and water. "X-factors," although osmotically active, are poor electroconductors.

Erythrocyte Potassium as an Aid in the Study of Potassium Depletion

By Donald A. Roth and Edwin G. Olmstead. Departments of Medicine, Marquette University School of Medicine and Milwaukee County General Hospital, Milwaukee. (Aided by a grant from the Wisconsin Heart Association.)

This work was undertaken to study erythrocyte potassium levels particularly in conditions in which the body stores of potassium would be expected to be low.

The erythrocyte potassium concentration was determined on blood specimens from 25 normal individuals. The method employed is based on the estimation of whole blood and plasma potassium by flame photometry and calculation of the erythrocyte potassium in mEq./L. of red cell mass. The normal range was from 87.4 to 97.3 mEq./L. with a mean of 91.5 and a standard deviation of 2.61.

Diseases studied included glomerulonephritis (7 cases), diabetes mellitus (4 cases), acute renal insufficiency (4 cases), and gastrointestinal loss of potassium (3 cases). It is apparent from the results that the level of the serum or plasma potassium does not represent the more important intracellular concentration. Remarkable depletion in erythrocyte potassium was found in patients with advanced chronic glomerulonephritis, reaching levels less than 75 mEq./L. in the terminal stages.

The erythrocyte potassium falls in renal insufficiency and may be very low, even though the serum potassium is high. Attempts to correct the hypokalemia (cells) and hyperkalemia (serum) of chronic glomerulonephritis are disappointing. This is contrasted with the patient with potassium depletion resulting from prolonged vomiting. In the cases of potassium loss from the stomach there is an accompanying alkalosis rather than acidosis and large amounts of potassium are usually required to correct the deficiency.

The data suggest that in conditions of acidosis or alkalosis there is a decrease in erythrocyte potassium which reflects loss of potassium from the body. The erythrocyte potassium level may have prognostic value in renal disease and may serve as a

guide to therapy in potassium depletion with alkalosis.

The Interpretation of Electrolyte Concentrations Obtained During Intravenous Electrolyte Infusions

By Carl R. Hines. Winnetka, Illinois.

In the management of patients with electrolyte abnormalities, an intravenous repair solution is often started before blood samples are obtained for analysis. The significance of the results of these subsequent electrolyte determinations is therefore questioned. This experiment was designed to study this situation in normal subjects prior to study of patients with electrolyte abnormalities.

500 ml. of a solution containing 155 mEq./L. of sodium chloride and 40 mEq./L. of potassium chloride were administered intravenously to each of 20 normal, fasting adults. This was given at a constant rate in exactly two hours. Blood was obtained from the opposite extremity prior to and 30, 60 and 120 minutes after the start of the infusion. The microhematocrit, and serum sodium, potassium and chloride concentrations were determined in each blood specimen.

The data were submitted to an analysis of variance. The following changes were found to be statistically significant at the 5% level: a decrease in the hematocrit and an increase in the serum potassium which persisted during the entire infusion; and an increase in the serum chloride concentration one and two hours following the start of the infusion. There was no significant change in the serum sodium concentration.

The maximal variations of the means were hematocrit, 3%; serum potassium, 0.38 mEq./L.; and serum chloride, 1.9 mEq./L. If true in abnormalities, as well, variations of this degree would be unlikely to alter the diagnostic appraisal. This demonstrates very rapid and nearly complete mixing of infused electrolytes in normals.

It is concluded that intravenous administration of sodium and potassium chloride at the concentrations and rate described to normal adults does not alter significantly the hematocrit or serum sodium, potassium and chloride concentrations in blood obtained during the course of the infusion.

Protein Metabolism in Infection

By Eric Reiss. Department of Medicine, Washington University School of Medicine, St. Louis.

The pattern of abnormal protein metabolism in acute infections was studied by use of isotope techniques. Pneumonia was induced in rats by intrabronchial instillation of Group A beta hemolytic streptococci. Animals serving as controls were intubated without instillation of microorganisms. All

animals were fed a normal diet until the time of the operation and were starved thereafter. N-15 glycine was given intraperitoneally either in divided doses for three days before the operation or as a single dose after the pneumonia was fully established. Animals were killed at intervals up to 160 hours. The proteins of the liver, kidney and spleen were measured for the total amount present and N-15 enrichment. In one experiment, N-15 concentration of muscle protein was also measured. Urines were analyzed for nitrogen and N-15 enrichment.

The urinary nitrogen excretion in animals with pneumonia was increased from 22 to 120%. The concentration of N-15 in the urine was lower but the total amount of N-15 in the urine was greater in the animals with pneumonia than in the control animals.

The N-15 concentration in the liver and kidney proteins was lower in the animals with pneumonia, both when the N-15 was given before and after the induction of pneumonia. In one experiment, the concentration of N-15 was also decreased in muscle protein in the animals with pneumonia. The total protein content of the livers of animals with pneumonia remained normal, while that of control animals decreased greatly. However, the total amount of N-15 in the liver was the same, in both groups, and the estimated turnover half time of liver protein was unaffected by pneumonia.

The predominant effect of infection appears to be a mobilization of amino acids from muscle to the liver. Under the conditions studied, net protein synthesis in the liver was actually stimulated.

The Clinical Importance of Ultrafiltrable Calcium Determination

By Anada S. Prasad and Edmund B. Flink.

Lack of a convenient method for ultrafiltration has been responsible for the paucity of clinical investigation of ultrafiltrable calcium. Since the ultrafiltration method reported by us was useful for this purpose, a large group of patients was investigated. Total and ultrafiltrable calcium, proteins and phosphorus were determined. In acidosis or alkalosis the pH was controlled during ultrafiltration, as described previously. Elevated values were found in hyperparathyroidism, some cases of multiple myeloma and metastatic cancer and acidosis without marked hyperphosphatemia. One patient with disseminated lupus erythematosus had normal total but elevated ultrafiltrable calcium, which led to the diagnosis of hyperparathyroidism and the surgical removal of a parathyroid adenoma. Decreased values were found in hypoparathyroidism, cases with hyperphosphatemia, idiopathic steatorrhea and some debilitated states. One patient had duodenal ulcer with pyloric obstruction, vomiting and alkalosis and frank tetany. He had normal total calcium but decreased ultrafiltrable calcium, which accounted for his tetany. In some cases of muscular dystrophy the percentage of ultrafiltrable calcium was decreased. In a few cases of hypoalbuminemia decreased total calcium with normal ultrafiltrable calcium was observed, which explained the absence of tetany in those cases. A comparison of determined ultrafiltrable calcium with that calculated from McLean-Hastings' nomogram or Ziesler's formula agreed well in normal cases, but poor agreement was found in abnormal cases. In cases with protein abnormalities, acidosis, alkalosis or hyperphosphatemia, a direct determination of the ultrafiltrable calcium should be performed, as the total calcium alone fails to show the changes.

GASTROINTESTINAL SYSTEM

A Clinical Test for Esophagitis

By Lionel M. Bernstein.

A controlled test was designed to elicit the symptoms of esophagitis by perfusion of the esophagus for 30 minutes with 200 ml. of 0.1 N HCl. Criteria were established to differentiate esophageal from gastroduodenal organs of experimentally induced symptoms.

Fifty-five subjects were studied. Results of the tests were related to esophagoscopic findings in 43 patients. A positive test elicited typical clinical symptoms in nine of ten patients with endoscopically demonstrable esophagitis; in ten of 12 patients with pseudoesophagitis (esophagitis by clinical history but without endoscopic abnormality); and in three of four patients with esophagitis by history who were

not examined esophagoscopically. A negative test (failure of acid perfusion to elicit symptoms) was found in 20 of 21 patients with neither history nor endoscopic findings of esophagitis; and in all of eight patients without history of esophagitis who were not examined endoscopically.

The test confirmed the esophageal origin of symptoms in patients with endoscopic evidence of esophagitis. It objectively demonstrated the esophageal origin of symptoms arising in esophagi with normal endoscopic appearance and with normal x-ray findings. The test effectively differentiated esophageal from cardiac pain.

That the test is a harmless diagnostic procedure is indicated by its failure to elicit symptoms in normal subjects; the lack of esophagoscopic abnormality induced by the test; the absence of either

electrocardiographic changes or cardiac pain in patients with coronary artery disease with or without angina; and the lack of recurrence of gastrointestinal bleeding in patients with recent gross bleeding episodes.

The high degree of success of this test in eliciting the symptoms of esophagitis as compared with the ineffective or inconsistent results of previous investigators must be attributed to both the longer duration of perfusion and the greater quantity of acid used.

Motor Function of the Distal Esophagus in Patients with Hiatal Hernia

By *E. Clinton Texer, Jr. and Hubbard W. Smith.*
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The relative contribution of the lower esophageal sphincter and the surrounding structures to the gastro-esophageal "closing mechanism" is not clear. A decrease in amplitude and prolongation of the deglutition complexes has been noted from the supradiaphragmatic area of patients with hiatal hernia. The supradiaphragmatic catheter tip should be adjacent to the lower esophageal sphincter in patients with rolling hiatal hernia, but below the sphincter in patients with sliding hiatal hernia.

Using a three-catheter system with the tips 5 cm. apart, deglutition complexes from 17 patients with rolling or sliding hernias and from 20 normal subjects were compared following "dry" and "barium" swallows. The deglutition complexes at 5 and 10 cm. above the diaphragm did not differ from the normal configuration. The supradiaphragmatic complexes from the hiatal hernia group were abnormal, but no differences in the parameters were noted between the rolling and sliding hernia subgroups.

The band of high pressure at the distal esophagus has been interpreted as being due to contraction of circular muscle fibers which represent a physiologic sphincter between the esophagus and stomach. Others have reported this zone to be present, corresponding to the level of the esophago-gastric junction, in patients with sliding hiatal hernias.

The recording technic employed did not enable us to detect this zone. However, the lack of normal progression of the high pressure zone in response to swallowing implies incompetency of the intrinsic esophageal sphincter in patients with hiatal hernia, in addition to the anatomic abnormalities affecting the esophago-gastric junction.

Effects of Atropine Sulfate and Propantheline Bromide on Stimulated Gastric Secretion

By *Adrian A. Kyriakopoulos, Robert Rock, Victor Rohrer and James A. Hagans.* Experimental Therapeutic Unit, Department of Medicine, University of Oklahoma School of Medicine, and V. A. Hospital, Oklahoma City.

The effects of atropine sulfate and propantheline bromide (Probanthine) were studied following gastric stimulation by parenteral histamine, caffeine, reserpine, and insulin.

Each of four groups of six healthy medical students received one of the stimulants alone as a control and later with atropine or Probanthine in random order upon successive weekly intervals. The inhibitor was given so that its "peak effect" coincided with that of the stimulant. The fasting stomach was emptied by intubation. After a 15 minute rest period, intermittent gastric aspiration was performed. Volume, concentration of HCl and total HCl secretion were determined on each specimen over a 3½ hour period. The mean peak values obtained in each control group were compared to the mean values obtained at a similar time in the same subjects after administration of the inhibitor. P values of <.05 were considered significant.

With 0.5 mg. of histamine base subcutaneously, atropine 1.0 mg. subcutaneously depressed the volume (mean difference, $\Delta = 22.7$ ml., $P < .05$) and total HCl secretion ($\Delta = 2.28$ mEq., $P < .02$). With Probanthine 30 mg. intramuscularly, only the total HCl secretion was significantly depressed ($\Delta = 1.89$ mEq., $P < .05$).

Atropine did not alter the response to reserpine 1 mg. intravenously, but Probanthine lowered the volume ($\Delta = 21.7$ ml., $P < .02$) and total HCl secretion ($\Delta = 2.11$ mEq., $P < .05$).

In the case of histamine and reserpine stimulation, the concentration of HCl was unaltered by either atropine or Probanthine.

When gastric secretion was stimulated by 12 units of insulin administered intravenously or by caffeine 500 mg. intramuscularly, however, both atropine and Probanthine markedly depressed the volume, concentration of HCl and total HCl secretion.

Thus parasympathetic inhibitors were capable of reducing parietal cell output as stimulated by all four agents.

Caffeine, like insulin, appeared to stimulate secretion of the alkaline component as well as HCl, while reserpine, like histamine, appeared to exert its stimulator effect only on parietal secretion.

The Effect of an Intravenous Fat Emulsion on Liver Function

By *Joann M. Gales, Anne U. Barnes and Jeanne Cooper.* Departments of Surgery and Pathology, V. A. Research Hospital and Northwestern University Medical School, Chicago.

A fat emulsion was given intravenously to ten patients with normal and to ten with abnormal bromsulphthalein retention.

Bromsulphthalein retention, thymol turbidity and flocculation, serum bilirubin, urine urobilinogen, total serum protein, albumen-globulin ratio, serum glutamic oxalacetic transaminase (GOT) and serum lactic dehydrogenase (LHD) were determined before, during and after courses of 14 to 18 consecutive daily infusions. Serum turbidity was measured daily by changes in optical densities. Liver biopsies were done in most patients before and after the course of fat infusions. The sections were stained by hematoxylin and eosin and by oil-red-O for fat.

One hundred ml. of the infusion contained 15 Gm. cotton seed oil, 4.0 Gm. of glucose, 1.2 Gm. of Pluronic F-68, and 0.3 Gm. of soybean phosphatide. The infusions were given over a two-hour period.

There was increased retention of bromsulphthalein during the course of the infusions as compared to preinfusion levels in both groups of patients. In most cases the dye retention returned to preinfusion levels within approximately two weeks after the infusions were stopped. Increase in thymol turbidity with return to preinfusion levels was also noted in both groups.

Occasional and inconsistent changes occurred in the cephalin flocculation tests. No changes in the other tests attributable to the fat emulsion were observed.

Increase in serum turbidity which persisted for more than 24 hours developed in eight patients during the time the infusions were given. In each case the turbidities returned to normal within a few days after the infusions were stopped.

Liver biopsies showed no changes in architecture and no abnormal accumulation of fat resulting from intravenous fat.

Potassium Depletion in Cirrhotic Patients

By Richard E. Peterson, Bartis M. Kent and James J. O'Toole. Medical and Radioisotope Services, V. A. Hospital, and the Department of Medicine, State University of Iowa, Iowa City.

Fluid and electrolyte metabolism of 10 cirrhotic patients with ascites, 10 cirrhotic patients without ascites, and 5 patients with acute hepatitis or fatty infiltration of the liver were studied and compared with 18 normal adult males. Total body water (TBW), extracellular fluid (ECF) and total exchangeable electrolytes (E_{Na} , E_K , E_{Cl}) were measured by the dilution principle using deuterium oxide, 6 hour sucrose infusions, and Na^{24} , K^{42} , and Br^{82} , respectively.

The 5 patients of the acute hepatitis group all had values in the normal range. The group of 20 cirrhotic patients, with and without ascites, had a mean E_K/L body water $>15\%$ below the mean for the 18 normals ($P < 0.05$). Comparing the cirrhotics

without clinical ascites with the normals, no significant difference was found in TBW or fat content. However, ECF averaged 20% larger in the non-edematous cirrhotics than in the normal group ($P < 0.05$). Consequently, intracellular water was decreased 6% in the nonedematous cirrhotic group. $E_K/Kg.$ of lean body mass in the nonedematous cirrhotics was $>20\%$ below the normal mean ($P < 0.02$), but the E_{Na} and E_{Cl} were insignificantly increased. The 10 with ascites had an insignificant increase in E_K over the 10 without ascites, but a great increase in E_{Na} and E_{Cl} . Two of the 6 cirrhotic patients autopsied were found to have kidney tubular changes compatible with potassium depletion.

The significant lowering of E_K cannot be explained by increased body fat. Cirrhosis was frequently but not invariably associated with E_K deficiency. Patients with low E_K showed serum potassiums both above and below normal. The lowering of E_K preceded marked sodium retention. Serial studies in cirrhotic patients showing clinical improvement were usually associated with increases in E_K .

These preliminary results suggest that further investigation of exchangeable potassium will give information of a major metabolic abnormality in cirrhosis.

Retrograde Hepatic Vein Occlusion in Man: Hemodynamic and Radiographic Studies

By Bernard L. Brofman. Cleveland.

This presentation is concerned with the non-operative determination of portal vein-hepatic vein pressure gradients, and with certain other practical hemodynamic and radiographic applications. As previously described for unilateral pulmonary artery occlusion in man, a special triple-lumen catheter, with an inflatable cuff over the middle lumen opening near the tip, is inserted via an arm vein, and advanced into the right atrium, inferior vena cava, and hepatic vein. Although "wedging" the catheter in the hepatic vein may provide an accurate estimate of portal vein pressure (Taylor and Myers), the method herein presented appears to be more reliable. When the catheter tip is in a large hepatic vein, with inflation of the cuff (with contrast material) producing complete occlusion of a segment of the hepatic venous circulation, the pressure in the segment distal to occlusion rises to a level exactly equal to the portal vein pressure. Instillation of contrast material into this occluded segment provides excellent visualization of the architecture of the hepatic venous circulation.

This method has been applied (without untoward effects) in more than 25 patients with the following conditions: (1) normal controls; (2) congestive heart failure, cardiac cirrhosis; (3) various degrees of hepatic cirrhosis; (4) metastatic carcinoma of the liver. This method has been applied to the hemodynamic evaluation of certain shunting pro-

cedures in the treatment of hepatic portal hypertension, and to the determination of the effects of certain pharmacologic agents upon hepatic blood flow.

Neonatal Hepatitis, a Genetic Study

By David Yi-Yung Hsia, Joseph D. Boggs, Shirley G. Driscoll and Sydney S. Gellis. Children's Memorial Hospital and the Departments of Pediatrics and Pathology, Northwestern University Medical School, Chicago, and the Department of Pediatrics, Boston University School of Medicine, Boston.

Neonatal hepatitis is a disorder of early infancy characterized by the onset of jaundice in the first weeks of life, dark urine, acholic stools, and moderate enlargement of the spleen and liver. Histologic examination of the liver reveals focal or widespread hepatocellular degeneration, often with the formation of multinucleated liver cells or liver "giant cells." Although an occasional case has been attributed to the transmission of an "inclusion cell" virus from the mother to the infant in utero, the etiology of the majority of cases is unknown. Erythroblastosis has been excluded in all instances by appropriate blood grouping tests.

A total of 50 families was studied from the genetic viewpoint with the following results: (1) Excluding the probands, there were 42 normal and 9 affected siblings. This was compared with a control group of 33 families with biliary atresia where there were 40 normal and no affected siblings, a difference which is highly significant ($X^2 = 7.9$ (1 d.f.)). (2) By the Weinberg sib method, $p = 31.8 \pm 6.0$ and by the proband method $p = 29.1 \pm 6.0$, both within the expected limits of a recessive mode of inheritance. (3) The condition has not been noted among the parents or collateral relatives. (4) There were 34 males and 19 females (sex not identified in 6 instances) among those affected, a sex ratio which is not significant ($X^2 = 1.6$ (1 d.f.)). (5) A study of birth order showed that five women had 7 normal offsprings, and one had 2 normal offsprings and then two affected infants; one had one normal offspring and then one affected infant; and six had seven affected infants after the first affected child.

While the present data do not rule out the possibility that neonatal hepatitis results from a changed intrauterine environment, it may also be consistent with the assumption of recessive autosomal inheritance.

The Effects of 5-Hydroxytryptophan, the Precursor of Serotonin, in Experimental Animals and Man

By John D. Davidson, Albert Sjoerdsma, Ladd N. Loomis and Sidney Udenfriend.

Previous experiments on the actions of serotonin in animals have been limited by its rapid transformation to inactive metabolites. Recent studies in this laboratory suggested that continuous elevations of tissue serotonin might be induced in vivo by administration of its precursor, 5-hydroxytryptophan (5HTP). It was found that injection of 200 mg./Kg. intraperitoneally into rats every twelve hours induced a sustained elevation of tissue serotonin. That prolonged elevations of serotonin were induced in man also is indicated by marked increases in urinary serotonin for as long as eight hours after intravenous infusion of 50 mg. of 5HTP.

Rats subjected to huge increases in tissue serotonin for periods up to four months exhibited several symptoms similar to those seen in patients with the malignant carcinoid syndrome, i.e., diarrhea, failure to gain weight, and a persistent "cyanotic" flush. Surprisingly, however, no significant pathologic anatomic changes, such as endocardial fibrosis, were observed. In eleven patients given 10 to 120 mg. of 5 HTP, no significant changes in blood pressure, pulse rate, respiration, pupil size, mental status or cutaneous vessels were noted. On the other hand, nausea or vomiting and urge to defecate were produced consistently, and increased small bowel motility was demonstrated by direct measurements of intraluminal pressures.

It is apparent from these studies that 5HTP is a potent new pharmacologic tool for studying the effects of prolonged increases in serotonin in humans as well as animals, and that the gastrointestinal tract, the largest body store of serotonin, is also the most sensitive organ system to the effects of this compound.

INFECTIOUS DISEASE

Natural Resistance to Respiratory Infections in Naval Recruits. I. Properdin Levels in Relation to the Immunization Program

By Irwin Schultz and Gene H. Stollerman. Naval Medical Research Unit No. 4, Great Lakes, Illinois.

The peak incidence of respiratory infections among military recruits has been observed consistently to occur during the first four weeks of training. An attempt was made to study alteration in natural resistance which might relate to this observation by serial measurement of blood levels of properdin.

Because properdin levels and host resistance have been altered experimentally by injection of lipopolysaccharides, the possible influence of immunization procedures upon properdin levels in naval recruits was investigated.

Blood samples were obtained from 12 volunteers prior to, and 24 hours after each inoculation, and then two weeks after completion of the series of immunizations against smallpox, diphtheria, tetanus and typhoid. Properdin levels were normal in all recruits at the beginning of the study (5-8 units). There was a significant fall in levels within the first few days, and by the end of the first week the mean titer was less than two units. It remained at this level through the fourth week, when the last inoculation was given. Two weeks later properdin levels had returned to normal values in 9 out of 10 recruits followed.

Study of 60 additional recruits selected at random throughout the training period confirmed the difference in properdin levels in the early and late weeks of training. A control group of 15 men who were not immunized was studied during the first two weeks of training and showed normal properdin levels. The possibility that immunization procedures lower properdin levels is suggested by these data and deserves further investigation. A controlled study of the effect of immunization procedures on respiratory disease rates is in progress.

Controlled Study of a Polyvalent Adenovirus-Influenza Vaccine

By F. Cox, Jr., E. A. Timm, J. M. Colville, E. L. Quinn and I. William McLean. Division of Infectious Diseases, Henry Ford Hospital, Detroit.

A controlled study concerning antibody response and tissue tolerance to polyvalent adenovirus-influenza vaccine was undertaken in November, 1956.

Three groups of approximately 37 individuals each were studied. Group I received fluid vaccine containing adenovirus types 3, 4 and 7, influenza type A (PR8, PR301 and swine) and influenza B (Great Lakes and Lee). Group II received a vaccine containing the same antigens which had been absorbed onto aluminum phosphate. Group III was given a placebo consisting of balanced salt solution. A single booster was administered 16 weeks after primary vaccination. Control prevaccination sera were drawn from all subjects at the onset of the program and thereafter at two, 16 (prebooster) and 18 weeks. Additional sera were obtained from one third of the subjects in each group at six, ten and 14 weeks. All sera were tested in tissue culture for neutralizing antibodies against type 3, 4 and 7 adenovirus. Influenza hemagglutination inhibition tests were performed on both control and post-vaccination sera.

The results showed that adenovirus antigen combined in an adenovirus-influenza vaccine elicited a satisfactory antibody response. The magnitude of the change in antibody titer was similar to that observed by Bell and co-workers when adenovirus antigen alone was employed. Aluminum phosphate absorbed vaccine produced superior antibody response when compared to the fluid vaccine.

Following a booster dose of polyvalent vaccine, increase in adenovirus antibody titer was noted only if the prebooster titer was fairly low or if the subject showed no antibody at the time of the booster. These results also indicated that the antibody titer resulting from vaccination was quite stable over an 18 week period.

Influenza hemagglutination inhibition antibody tests yielded an average arithmetic mean fold increase titer for all the contained strains of influenza virus of 0.3 in the control group and 4.5 and 3.9 in the two groups receiving vaccine.

No significant differences in the tissue tolerance were noted with the two types of vaccine.

Clinical Observations on the Use of Novobiocin in Penicillin-Resistant Staphylococcal Septicemia

By J. M. Colville, H. H. Gale, F. Cox and E. L. Quinn. Division of Infectious Diseases, Henry Ford Hospital, Detroit.

The seriousness of staphylococcal septicemia is indicated by a continuing mortality rate of 50 to 80%, despite modern antimicrobial therapy. Thus, new antimicrobial agents demonstrating antistaphylococcal activity are worthy of careful consideration and study.

Novobiocin, an antibiotic agent derived from *Streptomyces niveus* and demonstrating both in vitro and in vivo antistaphylococcal activity, became available for investigational study approximately two years ago. Subsequent investigations in our own and other laboratories indicated that this agent might prove useful in the treatment of staphylococcal sepsis due to penicillin resistant organisms.

During the past 20 months, seven patients with staphylococcal sepsis have been treated with Novobiocin. The following significant features were common to all cases and preceded the onset of staphylococcal sepsis in all cases: an underlying primary disease process, hospitalization, surgical intervention and previous exposure to various antimicrobial agents. In each instance the isolated strains of staphylococci were pigmented, hemolytic and coagulase positive.

Five of the seven patients responded satisfactorily to treatment with Novobiocin. Of the remaining two cases, one developed severe thrombocytopenia purpura—a previously unreported toxic reaction—on the ninth day of therapy and after receiving 18 Gm. Novobiocin. In the other patient,

emergence of a Novobiocin-resistant strain of staphylococcus occurred after seven days of therapy.

Serial Determination of Serum Glycoproteins in Pulmonary Tuberculosis

By Harold G. Muchmore, George W. Winkelman, James F. Hammarsten, Frances Felton, Jane B. Faulkner and Marvin Shellar. Medical Service, Laboratory Service and Research Laboratory, V. A. Hospital, and the Departments of Medicine and Biochemistry, University of Oklahoma, Oklahoma City.

The serum glycoprotein and seromucoid concentrations were determined as bound hexose in 43 patients with active pulmonary tuberculosis. The initial determinations were performed before or shortly after drug therapy was instituted. Patients were then followed serially during their course of treatment.

The glycoprotein concentration was expressed as a percentage of serum protein. The mean value was $2.33 \pm 0.06\%$, as compared to a normal value of $1.71 \pm .02$ based on 28 subjects ($t = 9.85$; $P < .01$).

Serum glycoprotein levels reflected the severity of the disease; far-advanced = 2.44 ± 0.08 , moderately advanced = $2.21 \pm 0.08\%$, minimal = 2.02 ± 0.07 . The presence of a cavity did not influence the serum glycoprotein concentrations, but the extent of lung tissue involved was related to glycoprotein elevations. Fever, previous treatment and erythrocyte sedimentation rate were not apparently related to the glycoprotein levels.

The serum glycoprotein declined to $2.07 \pm .045\%$ by the end of the third month ($t = 4.83$, $P < 0.01$). This decline was not related to x-ray improvement nor to sputum conversion. Some patients were followed one year, and the average glycoprotein level showed no further decline after the third month.

The seromucoid was $19.3 \pm 1.03 \text{ mg.}\%$ as compared to a normal value of $12 \pm 0.8 \text{ mg.}\%$ based on 11 normal subjects ($t = 5.62$, $P < .01$).

The seromucoid value was apparently not influenced by the extent of the disease, presence of cavities, fever, previous treatment or the erythrocyte sedimentation rate.

Seromucoid value declined to $14.7 \pm .87 \text{ mg.}\%$ ($t = 3.78$, $P < 0.01$) by the end of the third month. This decline was not related to x-ray improvement

or sputum conversion. Some patients were followed for one year and the average seromucoid values showed no further decline after the third month.

Serum glycoprotein and seromucoid concentrations are elevated in patients with active pulmonary tuberculosis and decline with chemotherapy.

The Effects of Blocking Drugs on the Vascular Reaction to Endotoxin in Cats

By Robert P. Gilbert. Department of Physiology, University of Minnesota Medical School, Minneapolis.

Histamine, 5-hydroxytryptamine (5-HT) and epinephrine have been suggested as mediators of the vascular responses to bacterial endotoxin. Chlorpromazine and Dibenzylamine, which block the effects of one or more of these drugs, have been shown to protect mice against the lethal effects of endotoxin. The present study concerns the effect of similar blocking drugs on the early vascular responses to endotoxin.

Carotid arterial pressures (CAP) and pulmonary arterial pressures (PAP) were measured in the open-chested cat under pentobarbital anesthesia. The administration of endotoxin to the cat characteristically caused a PAP rise and a CAP fall. Because antihistaminics and dibenamine did not block the vascular effects of large doses (0.1-1.0 mg./Kg.) of histamine and 5-HT, a dose of endotoxin was chosen which did not produce an overwhelming effect.

In fifteen control cats, .05 mg./Kg. of endotoxin caused a CAP fall of 45% ($\pm 9 \text{ S.E.}$) and a PAP rise of 73% ($\pm 17 \text{ S.E.}$). The combination of dibenamine (15 mg./Kg.) and pyrilamine (5 mg./Kg.) afforded almost complete protection in five cats: the CAP rose 3% ($\pm 7 \text{ S.E.}$) and the PAP rose 27% ($\pm 10 \text{ S.E.}$). In five trials of each agent alone there was only partial protection. The combination of LSD (0.5 mg./Kg.), with no adrenolytic activity, and pyrilamine gave fair protection in four cats: the average CAP fall was 12% and the average PAP rise was 15%. LSD alone mitigated the fall in systemic pressure, but did not alter the PAP rise. The effect of large doses of endotoxin (5 mg./Kg.) was not appreciably lessened by these drugs.

These results are consistent with the possibility that histamine and 5-HT are active during the early phase of the endotoxin reaction. It does not follow that the blocking agents used would be of therapeutic use, especially during the late phases of a severe endotoxin reaction.

KIDNEY

"Basal" Urine Volume as a Determining Factor in the Response of Healthy Subjects to Diuretics

By David C. Mock, Jr., Adrian A. Kyriakopoulos, Mervin L. Clark, Carl R. Doering and James A. Hagans. Experimental Therapeutic Unit, Department of Medicine, University of Oklahoma School of Medicine and V. A. Hospital, Oklahoma City.

Forty-two healthy subjects were observed on a metabolic ward for a continuous period of four days. Each subject received 3000 cc. of fluid, and a 2000 calorie diet containing 3.2 Gm. of sodium, 4.0 Gm. of potassium, and 4.0 Gm. of chloride. Weight before breakfast, total 24-hour urine volume, specific gravity, and room temperature and humidity were measured daily. On the first two days, observations were made without any agent being given. On the 3rd and 4th days each subject received a placebo or one of 3 diuretic agents administered by a double blind technique.

During the two preliminary days, urine volume varied greatly from subject to subject, but for each individual remained relatively uniform ($z = +.44$). No significant differences were noted between preliminary days, and days on which placebos were administered ($z = +.59$). When a diuretic was administered on the 3rd day, however, the differences between the 1st and 3rd day were highly significant ($P < .001$), but the striking thing was a dependable inverse ratio between the volume of urine excreted on preliminary day 1 and day 3, the first day of the diuretic ($z = -.65$). Those subjects who excreted less than 65% of their fluid intake in the urine on day 1 excreted large amounts of urine (more than 95% of fluid intake) under diuretic stimulation. Conversely, the greater the urinary output on day 1, the smaller was the response to the diuretic. Those whose preliminary urinary output was greatest failed to respond at all to the diuretic.

Effect in Change in Blood Flow Rate upon Renal Vascular Resistance

By F. Haddy, J. Scott, M. Fleishman and D. Emanuel. U. S. Army Medical Research Laboratory, Fort Knox, Kentucky.

It has long been known that renal vascular resistance increases as a function of artery pressure with levels in excess of 80 mm. Hg. This unique response has been variously ascribed to active vasoconstriction, passive vasoconstriction, absolute blood viscosity increase and dynamic blood viscosity increase. In an attempt to define the mechanism responsible for the resistance increase, the effect of changing flow rate in the range 25 to 180 ml./min. upon renal vascular resistance was studied in 82 pentobarbitalized laparotomized dogs. Flow rate was varied by interposing a pressure independent pump in the right renal artery. On the average, resistance decreased as a function of blood flow rate

with rates between 25 and 75 ml./min. and increased with rates between 75 and 180 ml./min. However, intraindividual and interindividual comparisons showed the onset of the resistance increase to be flow-rate independent but pressure-dependent. The onset always occurred at mean arterial pressures between 50 and 100 mm. Hg regardless of the flow rate. This relationship between resistance and pressure was unchanged by extrinsic nerve section, destruction of circulating catecholamines, local sympathetic nerve blockade, local parasympathetic nerve potentiation, increased CO_2 tension and $[\text{H}^+]$ and decapsulation. The resistance increase was abolished and replaced by a progressive resistance decrease during blood perfusion by intermittently using dextran as the perfusate, during dextran perfusion, and during blood perfusion in dead kidneys. Elevation of arterial pressure by increasing blood flow rate failed to significantly increase lymph flow rate from cannulated hilar lymph vessels. Winton, Gottschalk, Swann, and Miles have separately shown that elevation of renal artery pressure is accompanied by no or relatively little change in interstitial pressure. These observations indicate that the resistance increase results from active vasoconstriction due to a direct effect upon vascular smooth muscle of an increase in arterial transmural pressure.

Chlorothiazide—A Physiologic Connecting Link

By Archer P. Crosley, Jr. and Robert E. Cullen. Renal Section, Cardiovascular Laboratory, University of Wisconsin School of Medicine, Madison.

The purpose of this paper is to demonstrate in acute and chronic studies in 16 patients with renal and/or cardiac disease the manner in which chlorothiazide, a nonmercurial diuretic, serves as a physiologic connecting link between the activity of carbonic anhydrase inhibitors and the mercurial diuretics. Thus this agent, which inhibits carbonic anhydrase in vitro, is similar to acetazolamide, p-sulfamyl benzoic acid and dichlorophenamide in its ability to produce significant reductions in glomerular filtration rate ($p = <.01$) and renal blood flow ($p = <.001$), while simultaneously causing a significant increase in urinary pH ($p = <.01$) due to the increased excretion of sodium ($p = <.001$) and potassium ($p = <.01$). However, in contrast to C-A inhibitors, this compound, like the mercurial diuretics, is capable of producing a significant chloruresis ($p = <.01$) and diuresis ($p = <.001$). In a similar fashion, on chronic administration, a hypokalemic hypochloremic alkalosis may be observed rather than the hyperchloremic acidosis which may occur following the use of acetazolamide.

Therefore these results (1) establish a physiologic connecting link between the C-A inhibitors and the mercurial diuretics; (2) demonstrate the effectiveness of chlorothiazide as a valuable adjunct in the treatment of edematous states; (3) have physio-

logic significance when related to the renal mechanism involved in the excretion of water and electrolytes.

Laboratory and Clinical Observations on Chlorazinil, a Nonmercurial Orally Effective Diuretic Agent

By *J. B. Rochelle and Ralph V. Ford*. Departments of Medicine and Pharmacology, Baylor University College of Medicine, and the Medical Service, V. A. Hospital, Houston.

Chlorazinil (M-para-chlorophenyl-2,4-diamino-5-triazine hydrochloride) has been studied in men and dogs for its effect on the excretion of water and electrolytes and for its influence on renal hemodynamics.

Intravenously and orally in dogs there was a significant rise in sodium and water excretion at all dose levels of chlorazinil. The chronic oral administration in dogs of this agent effected a persistent water diuresis and a variable and lesser degree of natriuresis. There was no significant alteration in renal hemodynamics in dogs following either the intravenous or oral administration of this drug.

The electrolyte excretion pattern of chlorazinil in man showed primarily a significant increase in sodium, water and chloride excretion. There was a moderate increase in bicarbonate excretion and potassium excretion was sometimes increased while ammonia, phosphate and titratable acidity were depressed. The concentration of solute in terms of milliosmoles per liter was less than the concentration seen with comparably potent diuretic agents.

The chronic administration of chlorazinil in man showed continuous responsiveness until the sodium load had been depleted. This response was accompanied by no alteration in serum electrolytes. In man, the effective dose is between 300 and 600 mg. daily. It shows an onset of action within two hours following oral administration and a duration of action of approximately 18 hours. The potency estimation of chlorazinil in terms of natriuresis was calculated to be 0.49. In terms of water excretion, this agent has a potency estimation of 2.2, suggesting a greater effect on water excretion than with comparably potent diuretic agents (meralluride is 1.0).

This study shows chlorazinil to be a moderately effective nonmercurial oral diuretic agent. The mechanism of action of this agent, as reflected in its electrolyte excretion pattern, is different from mercurials, carbonic anhydrase inhibitors and chlorothiazide.

Depressed Renal Function in the Carcinoid Syndrome: Effects of Serotonin in Normal Subjects and of an Antiserotonin (Bromo-LSD)

By *Roland E. Schnneckloth, Irvine H. Page and A. C. Corcoran*. Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland.

Serotonin inhibits water diuresis in animals, and, in large doses, depresses glomerular filtration rate and urine flow. This report describes changes in specific renal functions in two volunteers during intravenous infusions of serotonin given alone or simultaneously with bromo-lysergic acid diethylamide (bromo-LSD), a potent serotonin antagonist in animals. Effects of bromo-LSD were also studied in two patients with the carcinoid syndrome and significant abnormalities of renal function.

Serotonin, 10–20 $\mu\text{g./Kg./min.}$, decreased C_{PAH} in two normal subjects; maximum rate of water reabsorption (T_{H_2O}) was unchanged. In two of three tests, potassium output increased and sodium output decreased. Decreases in $C_{Mannitol}$ were observed in two tests with corresponding decreases in urine flow. This sequence accords with that observed in animals given serotonin during osmotic diuresis. In two carcinoid patients, urinary outputs of 5-hydroxyindole acetic acid averaged 25 mg. and 239 mg. daily. Corresponding rates of C_{PAH} and $C_{Mannitol}$ were, respectively, 263 and 65 and 198 and 87 ml./min., indicating severe renal vasoconstriction; T_{H_2O} was at lower limits of normal. This renal ischemia was unassociated with hypertension, proteinuria, abnormal urinary sediment, or other abnormalities of renal function.

In both normal and carcinoid subjects bromo-LSD further depressed C_{PAH} . Contrary to previous reports, it provoked striking psychic disturbances, resembling those elicited by its congener, lysergic acid diethylamide; these aberrations may have contributed to the renal vasoconstriction.

Impairment of specific renal functions has not been described in the carcinoid syndrome but its occurrence is consistent with observations in animals that small doses of serotonin have variable effects on renal blood flow, while large amounts—such as may circulate in the carcinoid syndrome—cause severe renal vasoconstriction and even cortical necrosis.

NERVOUS SYSTEM AND MUSCLE

Changes in Body Composition During the Course of Acute Anterior Poliomyelitis

By *Alexander P. Remenichik, James A. Schoenberger and Josephine M. Dyniewicz*.

This study was designed to determine the changes in body composition which occur during the course of acute anterior poliomyelitis. One to four serial (at 7 to 10 day intervals), simultaneous measurements of total exchangeable potassium (K_e), anti-

pyrine space (TBW) and radiosulfate space (ECF) were made in 20 male and 24 female patients with acute poliomyelitis. From these data were calculated intracellular fluid volume (ICF), lean body mass (LBM), exchangeable potassium per kilogram of lean body mass (K_{LBM}), concentration of potassium per liter of cell water (K_{ICF}), ratio of extracellular fluid and intracellular volumes to antipyrine space $\left(\frac{ECF}{TBW}, \frac{ICF}{TBW}\right)$ and ratio of extracellular fluid volume to intracellular fluid volume $\left(\frac{ECF}{ICF}\right)$. Analysis

of the clinical courses did not reveal any significant differences between male and female patients.

K_e decreased during the course of the illness. Early in the illness, K_{LBM} for males (66.5 ± 10.2 mEq./Kg) was significantly greater ($p < 0.001$) than K_{LBM} for females (53.4 ± 7.7 mEq./Kg.). During the course of the illness, K_{LBM} decreased significantly for males and females, but by the third serial study there was no significant difference between males (45.3 ± 5.0 mEq./Kg.) and females (46.6 ± 3.1 mEq./Kg.). A significant difference ($p < 0.01$) for K_{ICF} was noted between males (141 ± 29.3 mEq./L.) and females (118 ± 24.7 mEq./L.) at the initial study. During the course of the illness K_{ICF} decreased for males (114 ± 21.2 mEq./L.) and was unchanged for females (119 ± 15.9 mEq./L.); however the decrease in K_{ICF} for males was not significant. There was a significant increase during the course of the illness in $\frac{ECF}{ICF}$ ratio both for males ($p < 0.005$) and for females ($p < 0.05$); the differences between males and females were not significant.

Significant changes in susceptibility and mortality have been demonstrated in animals inoculated with poliomyelitis virus after administration of gonadal and adrenal hormones. In man, mortality is significantly higher in males. Our observations suggest a mechanism for these experimental and epidemiologic data.

Differentiation of the Autosomal Recessive from the Sex-linked Recessive Type of Childhood Muscular Dystrophy

By Charles E. Jackson and Joshua H. Carey. Caylor-Nickel Clinic, Bluffton, Indiana, and Children's Hospital, Buffalo, New York.

A study of 14 cases (5 females, 9 males, ages 9 to 59) of an autosomal recessive type of childhood muscular dystrophy in one large kindred has emphasized certain features which help distinguish this type from the more common type of childhood muscular dystrophy seen only in boys and inherited as a sex-linked recessive disease. The various types of muscular dystrophy should be differentiated according to inheritance in clinical practice and in investigative studies, since the specific metabolic defect is likely to be different if inherited differently. The autosomal recessive disease tends to be of a later age of onset (6 to 13 years of age). It tends to be less rapidly progressive and compatible with a longer life span, which is of aid in prognosis. Pseudohypertrophy is less common in this type, although the muscle involvement is similar. The size of the QRS complexes of the electrocardiogram is not as great in this type as in the sex-linked recessive type. Data from the family history often provide the most important differentiating features.

RESPIRATORY SYSTEM

Diffusing Capacity of Pulmonary Membrane and Pulmonary Capillary Blood Volume in Normal Subjects; the Effects of Exercise and Body Position; Preliminary Observations in Cardiac Patients

By Benjamin M. Lewis, Tai-hon Lin, Richard Komisaruk and Frances E. Noe. Department of Medicine, Wayne State University College of Medicine and Detroit Receiving Hospital, Detroit.

A measurement of over-all diffusing capacity of the lungs by the single breath carbon monoxide technic depends on the thickness and area of the pulmonary membrane, the volume of blood in the capillaries and the rate at which this blood reacts with CO. To separate these two factors of membrane thickness and capillary volume, three measurements of total diffusing capacity are made at three different oxygen tensions. Reaction rate of CO with hemo-

globin is known approximately from in vitro experiments; its reciprocal, the resistance to diffusion due to reaction rate, increases linearly with oxygen tension. If the reciprocal of over-all diffusing capacity, which is the total resistance to diffusion, is plotted against reaction rate resistance, membrane diffusing capacity and capillary volume may then be estimated (Forster et al.). Twenty-two such measurements were made in 18 seated normal subjects. Average capillary volume was 89.0 ml., and average membrane diffusing capacity was 56.5 ml./mm. Hg/min. Capillary volume and membrane diffusing capacity are positively correlated with height, weight, body surface area, and vital capacity. Exercise in four normal subjects caused an increase of 15.9 ml. in capillary volume and 16.8 m./mm. Hg/min. in membrane diffusing capacity on the average. The recumbent position produced a mean increase in capacity volume of 26.8 ml. in four

normal subjects, but did not change membrane diffusing capacity consistently. The potential usefulness of estimating separately capillary volume and membrane diffusing capacity is illustrated by two patients with untreated congestive heart failure who showed an increased capillary volume, but a decreased membrane diffusing capacity, and one patient with mitral insufficiency, not in failure, who showed an increased capillary volume but a normal membrane diffusing capacity. Two of these patients showed a normal over-all diffusing capacity while breathing room air.

The Influence of the Pulmonary Capillary Blood Volume, Gas Tensions, and Hematocrit on Diffusing Capacity for Carbon Monoxide

By *John Rankin, R. S. McNeill and R. E. Forster.*
Department of Physiology and Pharmacology, University of Pennsylvania, Philadelphia, and the Cardiopulmonary Research Laboratory and Department of Medicine, University of Wisconsin, Madison.

Recently it has been shown that the diffusing capacity of the lung for CO depends not only on the physical properties of the alveolar capillary membrane but to a comparable extent depends on pulmonary capillary blood volume and on the rate at which erythrocytes within the pulmonary capillary bed can take up CO. If the diffusing capacity of the lung for CO (D_L) and the in vitro rate of combination of CO with intracorporeal hemoglobin (θ) are known for several different oxygen tensions, it is possible to assess the relative importance of these factors, and to determine the true diffusing capacity of the pulmonary membrane (D_M) and the pulmonary capillary blood volume (V_C). Studies were performed on 34 normal subjects and patients. An increase in alveolar oxygen tension decreased D_L without change in the physical property of the membrane, since O_2 competes with CO for hemoglobin. Hypercapnia increased D_L largely as a result of an increase in V_C . In patients with anemia and no evidence of pulmonary disease, D_L decreased as a result of a reduction in the pulmonary hematocrit and in some instances a marked reduction in D_M . In patients with diffuse interstitial pulmonary fibrosis or pulmonary emphysema, D_L decreased, owing in the main to a decrease in D_M , although in some instances there was also a reduction in V_C . In patients with pulmonary hypertension there was a proportionate reduction in D_M and V_C . In patients with pulmonary congestion as a result of heart disease the average D_L was normal, in spite of a reduction in D_M , owing to a considerable increase in V_C . These results indicate that the pulmonary capillary blood volume, gas tension, and hematocrit have a significant effect on pulmonary diffusing capacity for CO.

Blood Flow through a Distended Lung

By *Max H. Weil, Ward S. Fowler and Makoto Murao.* Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Others have proposed that increased intra-alveolar pressure compresses alveolar capillaries, and that this could be one cause of increased pulmonary vascular resistance in certain pulmonary diseases. Attempts to test this proposal were made on eight supine dogs anesthetized with pentobarbital sodium. The airways of the two lungs were separated by a double-lumen catheter; one branch thereof was tied within the lumen of the left main bronchus at thoracotomy. After thoracic closure and pulmonary re-expansion, the oxygen uptake of each lung was measured by double closed-circuit spirometry. The high oxygen content of inspired gas should ensure that the differences of oxygen content between mixed venous and pulmonary venous blood are equal for both lungs; therefore, the relative uptakes of oxygen should be proportionate to relative alveolar blood flow, and inversely related to relative vascular resistance, because of equal pulmonary arterial and left atrial pressures. The uptakes of oxygen were measured over 15-minute periods (1) for initial control, (2) after one lung had been distended to a mean airway pressure of about 20 cm. H_2O by the placing of a weight. During periods of increased unilateral airway pressure, the oxygen uptake of the distended right and left lungs averaged 132% (90-207), and 95% (37-198) of their respective control values. Therefore, alveolar blood flow of the single distended lung was not impeded in relation to that of the other lung, and occlusion of capillaries appears unlikely. When oxygen uptake of a single lung was increased during distension, it remained elevated after release of distension, until the other lung was distended. A significant but unexplained decrease of arterial oxygen saturation occurred in four of six dogs during distension of either lung.

The Effects of Chest Irradiation on Pulmonary Function

By *S. K. Sweeney, William T. Moss and Francis J. Haddy.* Departments of Medicine and Therapeutic Radiology, V. A. Research Hospital, Chicago.

Evaluation of pathologic and physiologic changes in the lung was made by determining pulmonary function studies before, and at various intervals after, irradiation to the thoracic cage of dogs. Data on 12 dogs is presented, each receiving as high as 3300 skin doses to each side of the chest as a single massive dose or fractionated over several months.

Ventilation and diffusion were evaluated after Nembutal anesthetization. A Lilly flow meter recorded expiratory and inspiratory velocity concurrent with intrathoracic pressure measured by eso-

phageal balloon. Functional residual capacity was determined by nitrogen-washout. The steady state carbon monoxide method provided values of the diffusing capacity. Arterial blood was drawn for CO_2 and O_2 tension by the Roughton-Scholander technic.

The dogs were paralyzed with succinyl-choline and respiration supported with a Bird pump. The diffusion studies were repeated. Further evaluation of compliance and resistance were made by inflating the lungs to predetermined values of pressure and comparing maximal velocity flow, esophageal pressure and volume of collected gas, after release of pressure through a 3 way stop cock.

Possible changes in pulmonary blood flow were evaluated in several of the dogs by measuring pulmo-

nary vascular resistance after catheterization of the pulmonary artery and vein. During the period studied there was no change from the normal in pulmonary vascular resistance. There was a consistent decrease in diffusing capacity with the passage of time after irradiation from control values of 5 to 1.5 mm./min./mm. Hg at 3 to 4 months. Compliance was decreased at higher pressures, but only slightly influenced at low pressures. Functional residual volumes regularly decreased.

The animals were killed preterminally and histologic sections were made of the lungs. The correlation of pathologic changes seemed consistent with the abnormalities developed in pulmonary function.

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